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SURGICAL ANATOMY OF THE SENSORY ROOT OF THE TRIGEMINAL NERVE

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The ancients made few contributions to the knowledge of neuralgic diseases in general and of facial pains in particular. Avicenna gave the first accurate description of facial neuralgia in the year 1000, but failed to recognize its relation to the fifth cranial nerve. He recommended treatment by scarification, blood-letting and aperients. Krause [1] mentioned that Van Swieten, about 1700, accurately described a case of neuralgia of the supra-orbital nerve, which he cured by the application of cinchona.

In 1756, André [2] described facial neuralgia as being due to a definite involvement of specific nerves, and it was he who first used the term tic douloureux. It remained, however, for John Fothergill,[3] an English physician, to give the first complete description of trigeminal neuralgia in his monograph on "Painful Affections of the Face." He suspected that "the cause of these extreme pains in the face might possibly be of a cancerous nature; the method of cure and other circumstances seem to corroborate the suspicion." Fothergill used extract of hemlock as a specific remedy.

The earliest record of the surgical treatment of trigeminal neuralgia is that of Schlichting [4] who, in 1748, sectioned the infra-orbital nerve for the relief of pain, with only temporary results. A short time later, von Laugier [5] advocated cauterization or section of the facial nerve by avulsion from the stylomastoid foramen. From that time until 1886, the accepted surgical treatment for this disease consisted of section of

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Read at the Fifty-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 7, 1932.

1. Krause, Fedore: Die Neuralgie des Trigemines nebst der Anatomie und Physiologie der Nerven, Leipzig, F. C. W. Vogel, 1896.

2. André, N., cited by Krause.[1]

3. Fothergill, John: Painful Affections of the Face, London, 1773, vol. 5, p. 129.

4. Schlichting: Examen von Land und Zee Chirurgie, Amsterdam, 1748, p. 92; cited by Krause.[1]

5. von Laugier: J. de méd., chir. et pharm., 1778, vol. 2; cited by Krause.[1]

the peripheral branches of the fifth cranial nerve. These operations were followed by disfiguring scars and recurrences of the pain. Almost simultaneously, Rose [6] in London and Edmund Andrews [7] in Chicago proposed and carried out an operation in which they excised the superior maxilla, trephined the base of the skull with the foramen ovale as a center and curetted the gasserian ganglion away. In the discussion of Rose's paper, Ferrier [8] stated that the pathology of neuralgia is obscure and that in many cases it may be of central origin. Section of the nerve above the ganglion might cause an ascending degeneration and thus lead to relief by producing atrophy of the center. Horsley [9] then suggested that the ganglion could be exposed more easily by a temporal approach, and he attempted to destroy its central connections by avulsing the posterior root from the pons.

In 1892, Hartley [10] and Krause [11] described the partial resection of the gasserian ganglion for the relief of trigeminal neuralgia by a transtemporal operation. In 1898, Spiller suggested and Frazier carried out an operation [12] in which the sensory root of the trigeminal nerve was sectioned near the gasserian ganglion. This suggestion of Spiller's has formed the basis for the present day surgical treatment of trigeminal neuralgia. Later, Frazier [13] described a method for identification and preservation of the motor root when the sensory root was divided.

More recently, Frazier developed the technic of saving the ophthalmic fibers of the sensory root in cases in which the pain did not involve that division. This procedure was based on observations of Frazier and Whitehead [14] which were made on human embryos. They stated that in its development the ophthalmic division is widely separated from the maxillary and mandibular divisions, which form very close to one

6. Rose, William: Removal of the Gasserian Ganglion for Severe Neuralgia, Lancet **2**:914 and 925, 1890.

7. Andrews, Edmund: Removal of the Gasserian Ganglion, J. A. M. A. **20**:180 (Feb. 18) 1893.

8. Ferrier, in discussion on Rose.[6]

9. Horsley, Victor: Remarks on the Various Surgical Procedures Devised for the Relief or Cure of Trigeminal Neuralgia (Tic Doulourex), Brit. M. J. **2**:1139, 1191 and 1249, 1891.

10. Hartley, Frank: Intracranial Neurectomy of the Second and Third Divisions of the Fifth Nerve, New York M. J. **55**:317, 1892.

11. Krause, Fedore: Resection des Trigemines innerhalb der Schädelhöhle, Arch. f. klin. Chir. **44**:821, 1892.

12. Spiller, W. G., and Frazier, C. H.: The Division of the Sensory Root of the Trigeminus for the Relief of Tic Douloureux; a Clinical Study with a Preliminary Report of One Surgically Successful Case (An Experimental Pathological and Clinical Study), Philadelphia M. J. **8**:1039 (Dec.) 1901.

13. Frazier, C. H.: Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **13**:378 (March) 1925.

14. Frazier, C. H., and Whitehead, E.: The Morphology of the Gasserian Ganglion, Brain **48**:458, 1925.

another, and, further, that the fibers of the sensory root run parallel, become arranged in separate bundles by the enveloping supporting tissue and do not tend to intermingle. They also noted that in the course of its development the gasserian ganglion rotates in such a way that its lateral surface finally becomes its dorsal surface. On a similar basis, Stookey [15] described an operative technic for the differential section of the sensory root.

Recently, von Nouhys [16] took exception to Frazier's conception of separate fiber bundles dividing the root into thirds. He found that the fiber bundles from the ganglion to the brain stem almost never run parallel, and in most of the adult roots he examined there were numerous irregular anastomoses of fibers near the hilus of the ganglion. Krause [1] had previously described this condition as a triangular plexus at the hilus. Sicard [17] confirmed these findings and called attention to the fact that they were first noted by Prochaska [18] in 1779.

In 1925, Dandy [19] suggested sectioning a selected part of the root near its entrance into the pons and later [20] described an operation by which the sensory root was exposed through a suboccipital approach. He stated that there is no accurate division of the sensory root into three anatomic subdivisions corresponding to the peripheral branches of the nerve, but that there is either a topographic rearrangement of the fibers or a change in their physiologic character or perhaps both. He concluded that, since the pain is cured in all divisions by section of the inferolateral portion of the root, there must be, in some degree at least, a distribution of fibers according to function. Dandy noted little or no permanent objective sensory loss following section of from three fifths to three fourths of the sensory root near its entrance zone into the pons. It might be assumed that it was possible to cure the pain of trigeminal neuralgia without the production of a loss of sensation in the face. Van Wagenen,[21] however, found localized areas of anes-

15. Stookey, Byron: Differential Section of the Trigeminal Root in the Surgical Treatment of Trigeminal Neuralgia, Ann. Surg. **87**:172, 1928.

16. von Nouhys, F.: Untersuchungen über die Zusammensetzung des Ganglion gasseri im Hinblick auf die operative Behandlung der Trigeminus-Neuralgie, Deutsche Ztschr. f. Chir. **227**:438, 1930.

17. Sicard, André: La neurotomie rétrogassérienne partielle dans le traitement de la neuralgie faciale, Paris, Librairie Louis Arnette, 1931.

18. Prochaska: De structura nervorum, Vienna, R. Græffer, 1779, p. 104; cited by Sicard.[17]

19. Dandy, W. E.: Section of Sensory Root of Trigeminal Nerve at the Pons. Preliminary Report of Operative Procedure, Bull. Johns Hopkins Hosp. **36**:105, 1925.

20. Dandy, W. E.: Certain Functions of the Roots and Ganglia of the Cranial Sensory Nerves, Arch. Neurol. & Psychiat. **27**:22 (Jan.) 1932.

21. Van Wagenen, W. P.: Some Indications of Section of Posterior Root of Trigeminal Nerve Through Posterior Fossa, Ann. Surg. **45**:1013, 1931.

thesia in two cases in which only the lower half of the nerve was sectioned by this method.

In view of these apparent contradictions it has been our object to study the embryology, physiology and neuro-anatomy of the sensory root of the trigeminal nerve in relation to the surgical treatment of trigeminal neuralgia.

EMBRYOLOGY

From the developmental standpoint, His [22] noted in the human embryo that "as all nerves coming from peripheral ganglionic beginnings, so the trigeminal in its root piece arises out of bundles with a crossed course; the posterior bundle going forward, the anterior going backward, the medial bundle going lateralward and the lateral, medialward." Windle [23] has confirmed His' view. He found in cat embryos that the entrance zone of the fibers from the anteriorly developing ophthalmic division of the ganglion is posterior and somewhat medial to the entrance zones of the fibers entering the brain stem from the mandibular and maxillary divisions of the ganglion. The photomicrographs furnished to us by Windle (fig. 1, *A*, *B* and *C*) are taken from a series of sagittal sections through a 10 mm. cat embryo. *A* is the most lateral and *C* the most medial section. Four sections intervene between *A* and *B*, and five sections between *B* and *C*. The arrangement of the fibers already outlined is evident.

It would appear further that, as development continues, rotation of the ganglion takes place so that the lateral aspect of the ganglion comes to lie dorsally, as Frazier and Whitehead stated. The ophthalmic portion then lies medial and slightly superior to the maxillary, with the mandibular portion lateral and slightly posterior to the latter. At the same time the brain stem rolls up about its long axis and assumes its adult state. The relationships then change so that the entrance zone of the fibers arising from the ophthalmic portion of the ganglion is in the inferior and medial region of the root. Similarly those fibers from the mandibular and maxillary portions of the ganglion occupy mainly the lateroposterior portion of the entrance zone. The latter fibers, therefore, overlie the ophthalmic fibers. Figure 2 is a diagrammatic drawing based on the facts gained from a consideration of this embryologic evidence. For purposes of orientation it must be remembered that the entrance zone of the sensory root into the brain stem, in the adult human being or cat, is somewhat elliptic or oval. Its long axis is in a plane which makes an angle of about 30 degrees with that of the long axis of the

22. His, Wilhelm: Die Entwickelung des menschlichen Rautenhirns vom Ende des ersten bis zum Beginnen des dritten Monats, Abhandl. d. math.-phys. Classe d. k. sächs. Gesellsch. d. Wissensch., Leipzig **17**:62, 1890.

23. Windle, W. F.: Personal communication to the authors.

brain stem, and its plane of cross-section faces somewhat lateral to the plane of cross-section of the pons.

This rotation of the sensory root fibers is grossly apparent on removal of both human and animal specimens of the brain and sensory root with the gasserian ganglion intact. The mandibular

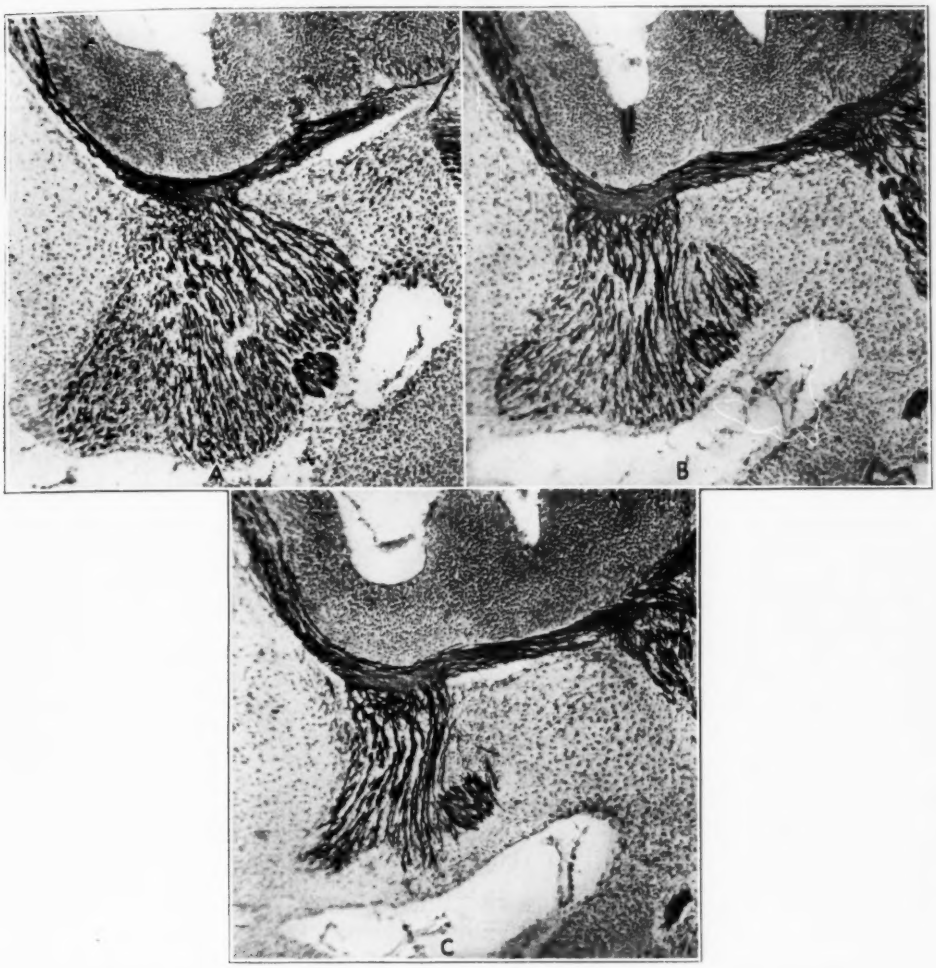


Fig. 1.—Sagittal sections of a 10 mm. cat embryo (pyridine silver stain) showing fibers of the sensory root of the trigeminal nerve: *A*, fibers of the mandibular division; *B*, fibers of the maxillary division; *C*, fibers of the ophthalmic division. In each section the rostral aspect is to the left.

portion of the ganglion tends to turn up so that the ganglion comes to lie against the brain stem with the mandibular portion dorsal and the ophthalmic portion ventral. In figure 3 the relations are apparent.

When the parts are fixed so as to preserve the relationships existing in life (3 *a*) and the longitudinal sections of the root and ganglion are made in the plane of the ganglion, the definite crossing of the fibers due to rotation can be seen clearly. When the parts are fixed as they naturally tend to lie after removal (3 *b*) and the sections likewise made in the plane of the ganglion, the straight untwisted and uncrossed appearance of the fibers from the ganglion into the brain stem is noted.

Thus from the developmental standpoint there is evidence that the fibers of the sensory root of the trigeminus do not pursue a straight parallel course from the ganglion into the brain stem. Rather, there are crossing and anastomoses of the fibers and a clearly defined rotation.

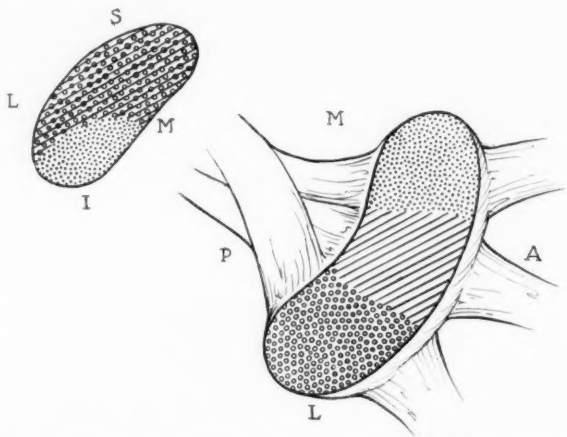


Fig. 2.—Diagrammatic representation of gasserian ganglion and entrance zone of sensory root in the adult human being based on embryologic data: *L*, lateral; *M*, medial; *I*, inferior; *S*, superior; *P*, posterior, and *A*, anterior.

PHYSIOLOGY

Gasser and Erlanger,[24] working with the cathode ray oscillograph and nerve blocks by pressure and cocaine, furnished conclusive evidence that the unmyelinated and the smallest myelinated fibers conduct pain stimuli, while the larger myelinated fibers conduct touch stimuli. Windle [25] investigated the distribution and probable significance of the unmyelinated nerve fibers in the sensory root and the branches of the trigeminal nerve in the cat. He found those nerves concerned primarily with the transmission of painful impulses, such as the branches to the

24. Gasser, H. S., and Erlanger, J.: The Rôle of Fiber Size in the Establishment of a Nerve Block by Pressure or Cocaine, Am. J. Physiol. **88**:581, 1929.

25. Windle, W. F.: The Distribution and Probable Significance of Unmyelinated Nerve Fibers in the Trigeminal Nerve of the Cat, J. Comp. Neurol. **41**:453, 1926.

cornea, to be composed largely of small myelinated and unmyelinated fibers, while those concerned with more diversified sensory impulses, such as the cutaneous branches, had a relatively higher percentage of large myelinated fibers. In the sensory root of the cat he found that the small fibers were distributed evenly but tended to occur in groups scattered throughout the root. They were somewhat more abundant about the periphery of the root.

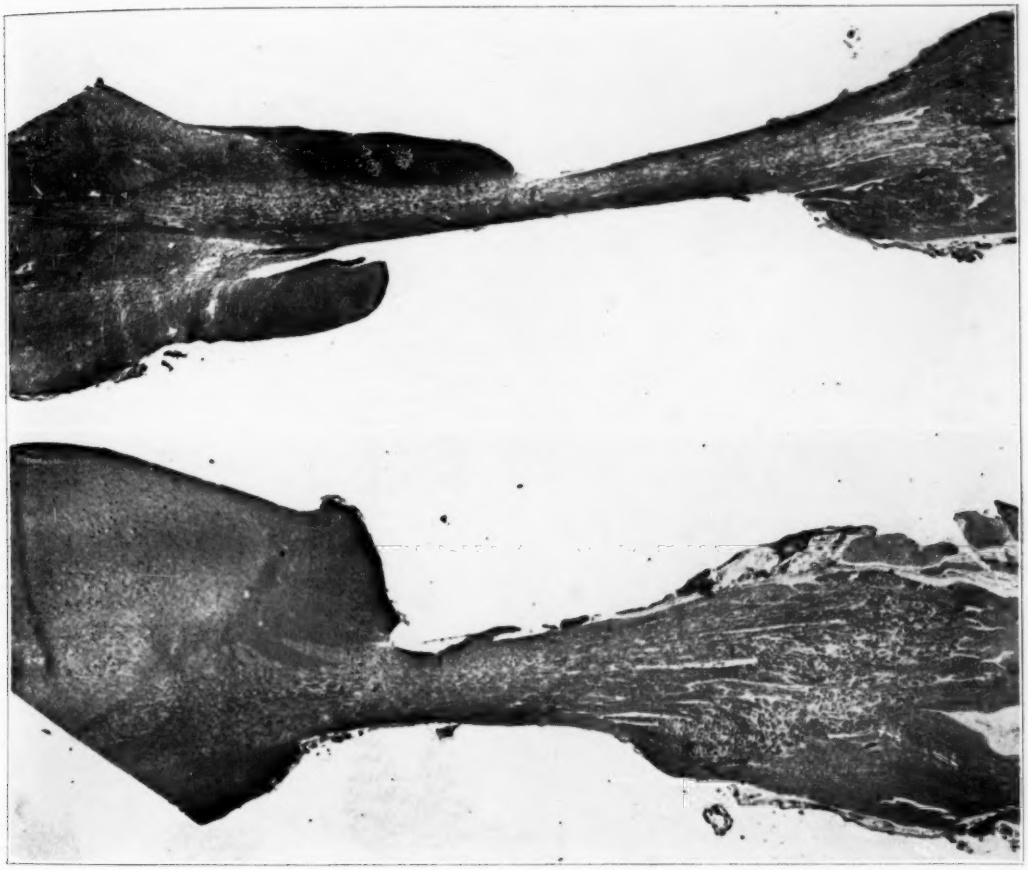


Fig. 3.—Longitudinal sections of gasserian ganglion, sensory root and entrance zone (Davenport stain). The structures were fixed as they are related during life (above) and as they naturally tend to lie after removal (below).

The work of Ranson [26] on the cat and of Ingvar [27] on human beings shows that just before the dorsal root of a spinal nerve enters the cord

26. Ranson, S. W.: Cutaneous Sensory Fibers and Sensory Conduction, Arch. Neurol. & Psychiat. **26**:1122 (Dec.) 1931.

27. Ingvar, Sven: Zur Morphogenes der Tabes, Acta med. Scandinav. **65**:645, 1926-1927.

the unmyelinated fibers separate from the myelinated ones and arrange themselves at the periphery of each small radicle into which the root has divided. As the rootlet enters the cord, the central bundle of myelinated fibers runs over the apex of the posterior horn into the posterior funiculus, and the peripherally placed unmyelinated fibers

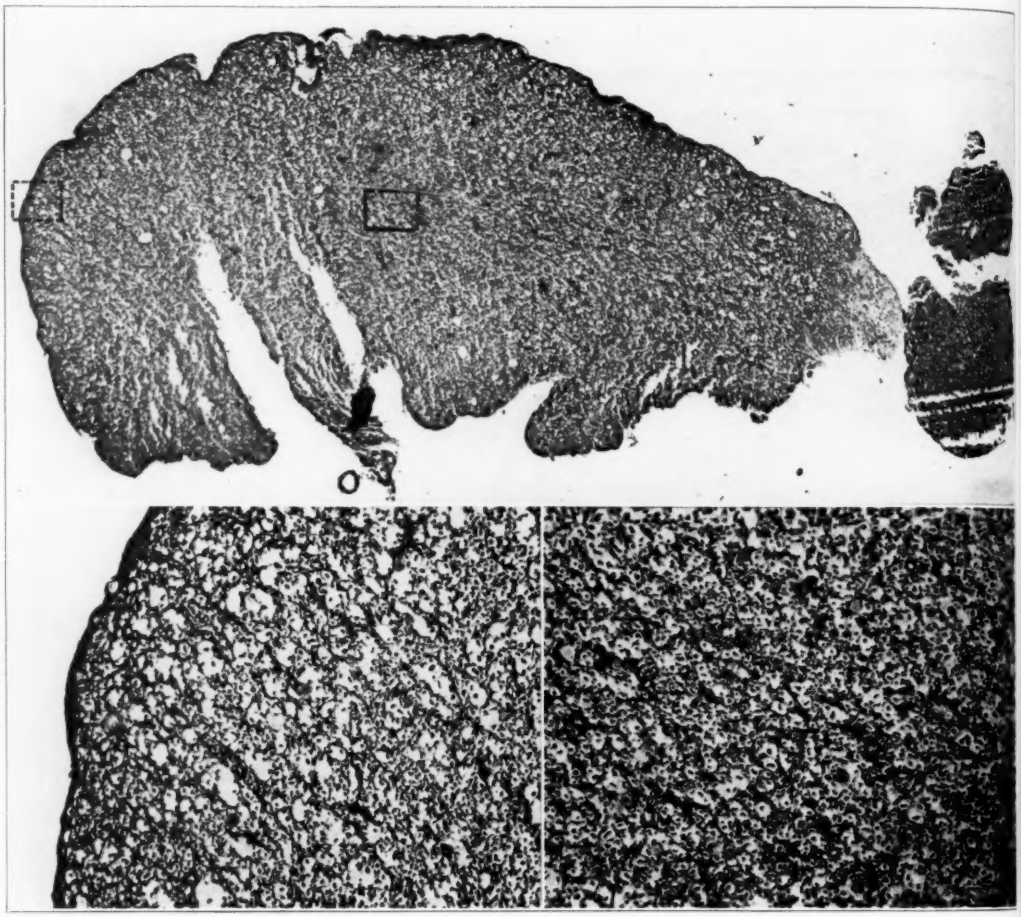


Fig. 4.—Photomicrographs of the sensory root (human) at its entrance zone into the pons (above). Higher power photomicrographs of the areas blocked out are shown below. The regular distribution of the larger and smaller fibers is evident both at the periphery and at the center.

turn laterad into the tract of Lissauer. It was concluded that these fibers carry impulses of pain.

With these facts in mind we have studied cross-sections of the sensory root of the trigeminal nerve from both cats and human beings. The sections were stained with Davenport's silver technic, which gives

a sufficiently clear differentiation between myelinated and unmyelinated fibers to permit of accurate differential counts. In these cross-sections, both from human beings and from cats, we could see that the small and large fibers are more or less regularly intermingled without any definite arrangements into topographic divisions. This is true in the sections near the ganglion as well as in those near the brain stem. If anything, in the sections from human beings the large myelinated fibers seemed to be in relative predominance about the periphery, as opposed to Windle's findings in the cat. Figure 4 illustrates a cross-section of the entire sensory root of man, as well as high powered photomicrographs of the central region and the inferolateral region of the entrance zone, the part sectioned by Dandy. It shows clearly the absence of any definite topographic arrangement of fibers in the sensory root of the trigeminus.

We are, therefore, unable to substantiate any theories of topographic rearrangement of fibers in the sensory root near the brain stem on a functional basis. As nearly as we are able to conclude from this study, there is no physiologic foundation for any operations aimed at the differential interruption of certain functions by partial section of the sensory root near the brain stem.

NEURO-ANATOMY

The observations of von Nouhys, Krause, Sicard and Prochaska on the gross anatomy of the sensory root of the trigeminus have already been mentioned. Our dissections of ten human sensory roots tend to confirm their findings. Figure 5 shows the plexus-like meshwork of the fiber bundles as they leave the ganglion. The numerous ramifications of the rootlets in their course to the entrance zone is evident. These anastomoses of the fasciculi of the root are also apparent in the longitudinal sections of the sensory root in the cat, as shown in figure 3.

In degeneration experiments performed on rabbits, Bregman [28] found that when the sensory root of the fifth nerve was degenerated completely at its entrance into the pons, the descending spinal root was likewise fully degenerated; when only the medial portion of the entrance zone was degenerated, only the ventral portion of the descending tract was degenerated, and when only the lateral portion of the root at its entrance was degenerated, only the dorsal portion of the descending tract was involved. In animals in which the degeneration was in the ventral part of the spinal tract there was an absent corneal reflex on the same side, with marked keratitis. When only the dorsal portion of the tract was degenerated, the corneal reflex was conserved and keratitis was

28. Bregman, E.: Ueber experimentelle aufstiegende Degeneration motorischer und sensibler Hirnnerven, Arb. a. d. Inst. f. Anat. **1**:73, 1892.

absent. In a dog with partial section of the sensory root, Spiller and Frazier [12] found the lateral portion intensely degenerated at the entrance into the pons, while in sections of the medulla these degenerated fibers seemed to occupy the dorsal portion of the descending spinal root.

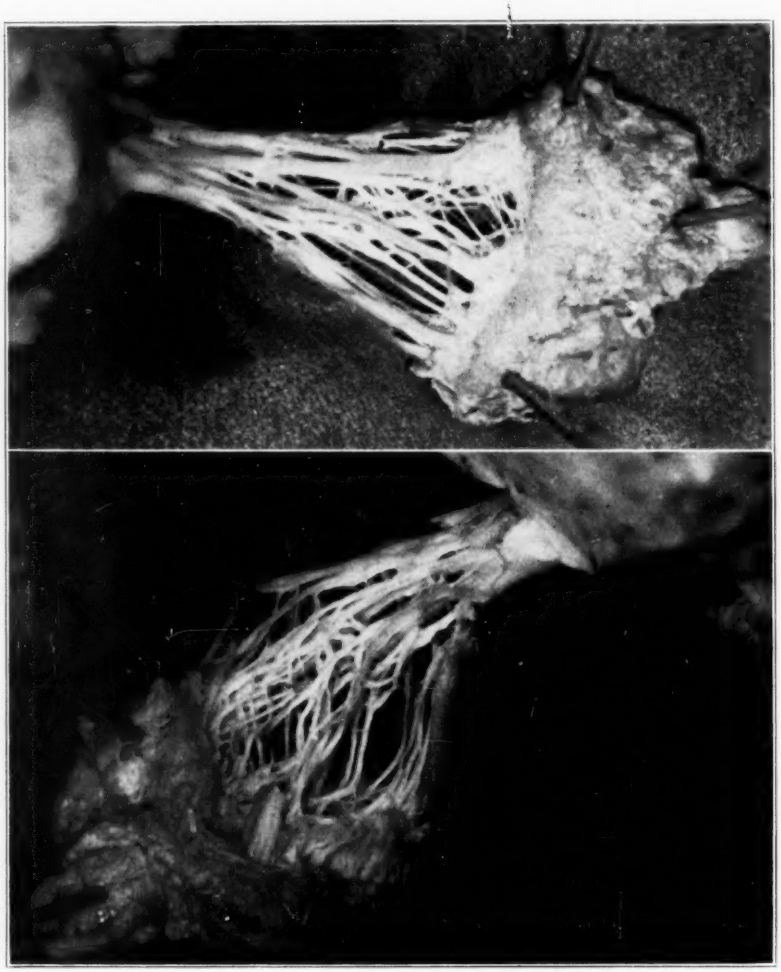


Fig. 5.—Photographs of gross dissections of the sensory root (human) from the superior and inferior surfaces.

We have performed degeneration experiments on sixteen cats, which may be outlined as follows:

After making both complete and partial sections of the sensory root, the cats were allowed to recover and were observed for from two to three weeks. They were then killed by bleeding; the brain stem, together with the sensory root and

gasserian ganglion, was removed in toto, fixed in Mueller's fluid, impregnated with osmic acid after the method of Marchi and sectioned serially so that the site of section could be checked and the degenerations could be followed in their entire extent. Figure 6 shows diagrammatically the sites of the partial sections.

In all instances in which the sensory root had been sectioned completely, either near the ganglion or just before its entrance into the pons, keratitis developed and the animals did not react to painful cutaneous stimuli, either by pin prick or by painful faradic current, over the entire peripheral distribution of the fifth cranial nerve on that side. They did react to the same stimuli on the contralateral side of the face. In each of these animals there was a complete picture of Marchi degeneration of the entire descending tract of the trigeminus which was traced down as far as the first cervical segment of the cord.

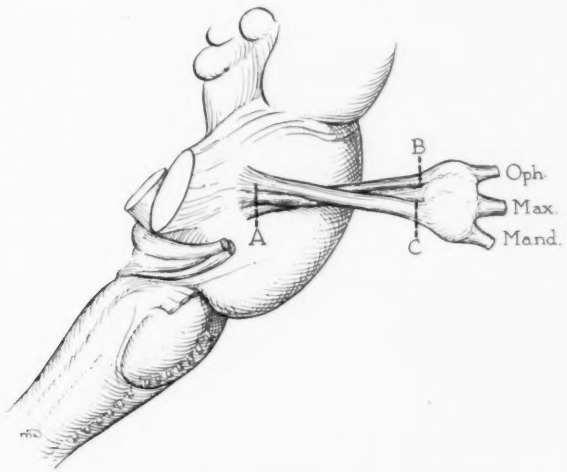


Fig. 6.—Diagram showing the location of the sections of the sensory root which were performed on experimental animals.

After section of the inferior and lateral two thirds of the sensory root (fig. 6, *A*) near its entrance into the pons, as nearly as possible the procedure described by Dandy, there was absence of the corneal reflex, and keratitis developed. The animals did not react to painful stimuli over the areas of the maxillary and ophthalmic distributions on the homolateral side. They reacted, however, over the entire trigeminal distribution on the opposite side and about the lower jaw and the mucous membrane of the lower lip on the same side. In the Marchi-stained preparations of these specimens there was degeneration in the ventral two thirds of the spinal tract in the more rostral sections. In passing down the brain stem the degeneration included an increasingly greater portion of the tract until in the lowest sections almost the entire tract was involved (fig. 7).

When we sectioned only the fibers that arise in the ophthalmic portion of the ganglion close to the ganglion (fig. 6, *B*), keratitis likewise developed in the homolateral eye after recovery from the operative procedure. There was also absence of the corneal reflex on the same side. These animals did not respond to painful stimuli about the eye or in the supra-orbital region on the homolateral side, but they did respond to stimulation over the cheek and the lower lip on the same side as well as over the entire contralateral half of the face. The degeneration in these animals was found to involve only the inferior and medial portions of the entrance zone. In the upper part of the spinal tract only the ventral portion was degenerated. While the area involved was not

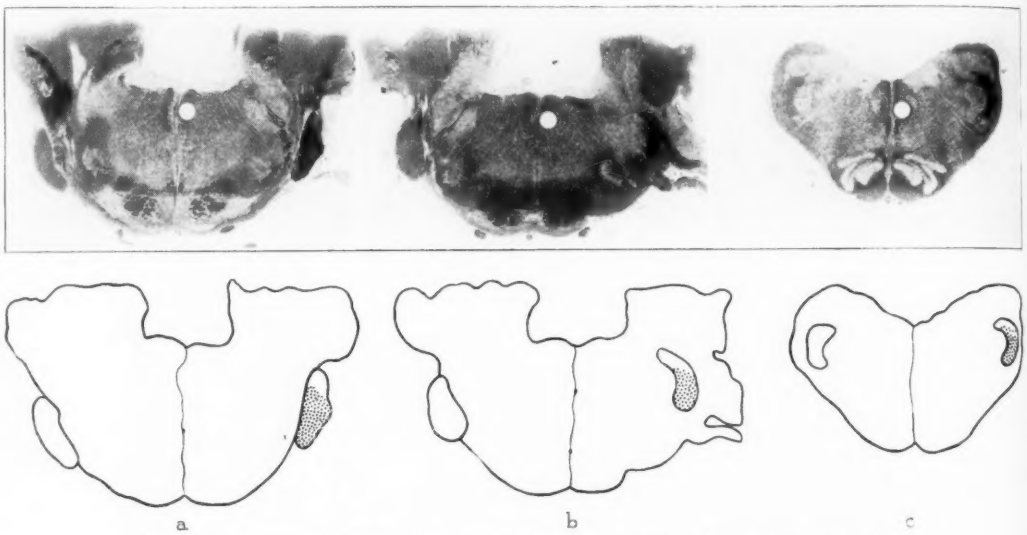
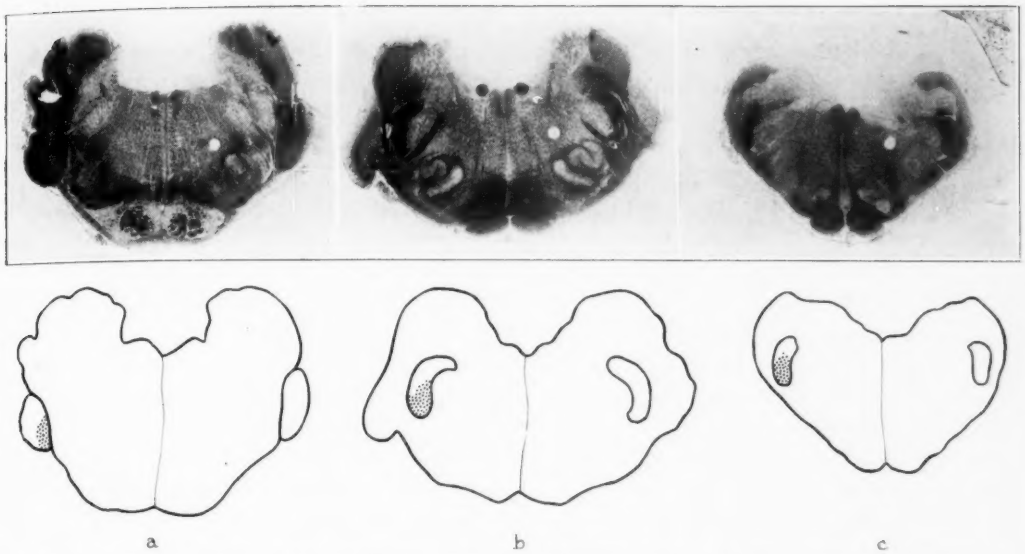


Fig. 7.—Cross-sections of the brain stem of a cat following section of the sensory root near the entrance zone (fig. 6 *A*) (Marchi stain): *a*, level of entrance zone; *b*, level of facial nucleus; *c*, level of superior border of inferior olive.

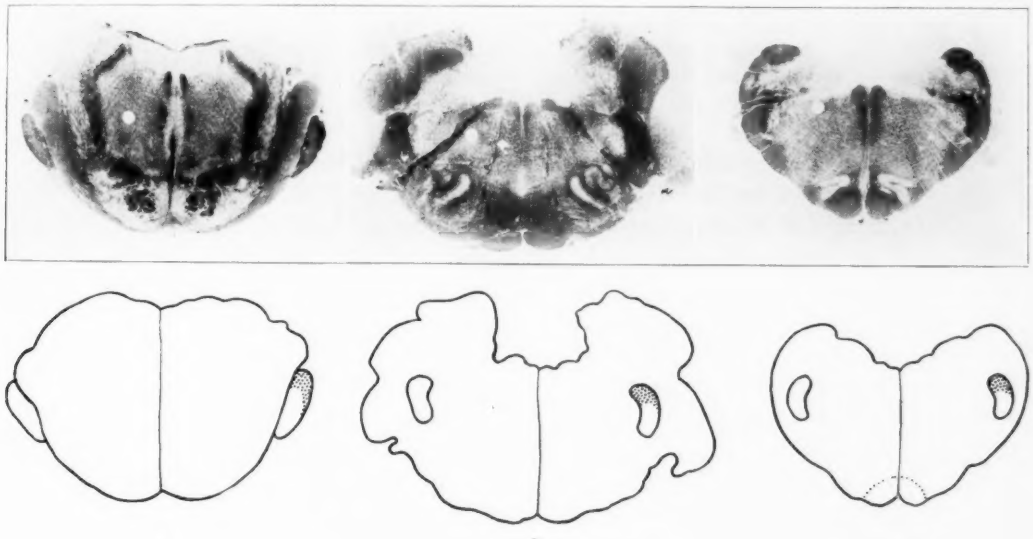
so great, there was noted, as in the previous specimens, a tendency for the degeneration to involve a larger proportion of the tract as it was followed down the brain stem. It was traced as far caudad as the first cervical segment of the cord (fig. 8).

In still other animals only the fibers that arise from the mandibular portion were sectioned in close proximity to the ganglion (fig. 6, *C*). In none of these animals did postoperative keratitis develop. The corneal reflex was conserved. They reacted to painful stimuli over the areas supplied by the ophthalmic and maxillary divisions of the trigeminal nerve on the same side but did not react about the lower lip on that side. They reacted normally over the entire opposite side of the face. The degeneration in the animals was found to involve the superior part of



a b c

Fig. 8.—Cross-section of the brain stem of a cat following section of the ophthalmic portion of the sensory root close to the ganglion (fig. 6 *B*) (Marchi stain): *a*, level of entrance zone; *b*, level of facial nucleus; *c*, level of superior border of the inferior olive.



a b c

Fig. 9.—Cross-sections of the brain stem of a cat following section of the mandibular portion of the sensory root close to the ganglion (fig. 6 *C*) Marchi stain): *a*, level of entrance zone; *b*, level of facial nucelus; *c*, level of superior border of inferior olive.

the lateral aspect of the entrance zone of the root. In the more rostral sections through the medulla it involved the dorsal portion of the descending tract. On passing down the brain stem it continued to occupy a relatively similar position but diminished somewhat in its extent in the lowest sections (fig. 9).

If, on the basis of the foregoing degeneration experiments, we attempt a rough diagrammatic representation of the topographic anatomy of the sensory root only in its course from the ganglion to the brain stem, figure 10 is the result. It is interesting to compare it with figure 2, which was based on the developmental anatomy.

From these studies it is evident that, although there are no clearly defined funicular components in the sensory root at its entrance into the pons, and although there are numerous anastomoses along the course of the root, the fibers which come from the various divisions of the gasserian ganglion appear to occupy a definite position in the root in the region of its entrance zone. The fibers from the ophthalmic division lie

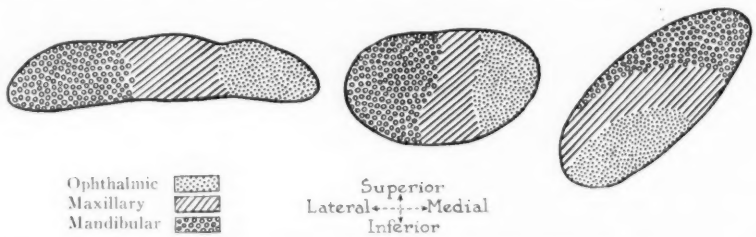


Fig. 10.—Diagrammatic representation of the topographic anatomy of the sensory root (human) in its course in the ganglion to the entrance zone based on degeneration experiments.

in the inferior and medial position. The fibers from the mandibular division occupy the superior and lateral position and those from the maxillary division occupy the intermediate area.

COMMENT

In the hands of the majority of neurologic surgeons the mortality rate from the operation through the temporal bone for the division of the sensory root is less than 1 per cent. There has been a single death in a series of 156 operations for trigeminal neuralgia performed by one of us (Davis).

There are, however, certain postoperative complications which are disturbing. In this same group of patients facial weakness developed in 6 patients in from twenty-four hours to seven days after operation. In all of these patients the facial movements were recovered completely in from two weeks to ten months. In 7 patients of this series an irritation of the cornea, followed by a small scar, has developed. In each instance

direct trauma of the cornea was the exciting factor. Each patient has varying complaints about the loss of sensation in the face, depending on his ability to adjust himself to the sensory loss. Any operative procedure which will improve the present results of the surgical treatment of trigeminal neuralgia would be welcomed. However, such a technical improvement should have a sound anatomic and physiologic basis.

From the degeneration experiments we have performed, the histologic structure of the sensory root and the gross dissections which have been made, it seems evident that division of the inferior portion of the sensory root at its entrance into the pons would sever the fibers of the ophthalmic portion of the ganglion. If three fourths of the inferior portion of the root were severed by a suboccipital approach, as has been recommended, most of the maxillary and a few of the mandibular fibers would also be sacrificed. On the other hand, if only a small section of the inferior portion of the root were made, a small number of the ophthalmic fibers would be severed and a rather large proportion of the mandibular and maxillary fibers would be left intact. Only under this condition, in the light of our investigations, is it conceivable that sensation can be conserved over most of the area supplied by the trigeminal nerve. It remains to be proved whether or not the pain of trigeminal neuralgia can be relieved permanently under such conditions.

The plexiform arrangement of the radicals in the root makes it evident that, if a subtotal, or differential, section of the sensory root is performed, it should be done very close to the ganglion to make certain that all of the fibers of the desired division are sectioned.

CONCLUSIONS

1. There are numerous anastomoses between the fibers in the sensory root of the trigeminal nerve near the hilus of the gasserian ganglion.

2. There is no topographic distribution of fibers in the sensory root which might be interpreted as an arrangement according to the type of sensation transmitted by them.

3. There is a definite rotation of the sensory root in man and in animals between the gasserian ganglion and the pons.

4. Experimental section of the ophthalmic division of the ganglion and of the inferior portion of the sensory root immediately adjacent to the pons results in an identical microscopic picture of degeneration in the pons. Section in both instances is followed by a loss of corneal sensation and keratitis.

DISCUSSION

DR. CHARLES H. FRAZIER, Philadelphia: With regard to the physiology of the sensory root, it has been known for a long time that the root is composed of both myelinated and nonmyelinated fibers, the former carrying tactile and the latter pain sensation. But it remained for Dr. Davis and his associate, Dr. Haven,

to demonstrate that there was no topographic rearrangement of these fibers in the sensory root on a functional basis, and therefore no physiologic foundation for any operation aimed at the differential interruption of pain stimuli alone by a partial section of the sensory root near the brain stem.

The investigations of Bregman (1892), of Spiller (1901 and 1904) and of van Gehuchten (1903), cited by Davis and Haven, have determined by the method of recent degeneration following partial section of the sensory root, or the tearing out of peripheral divisions of the trigeminal nerve, that throughout this nerve to its termination as the spinal root in the pons and medulla oblongata the nerve fibers maintain a definite relationship to the three peripheral divisions. Furthermore, these investigations, carried out more than forty years ago, have demonstrated that at the entrance of the sensory root into the pons the lower and probably the lower median fibers of the sensory root represent those fibers which are concerned with the ophthalmic branch, whereas the upper and upper-lateral fibers represent those fibers which are concerned with the mandibular and maxillary divisions of the peripheral nerve distribution. It is especially gratifying to find that Davis and Haven in their careful work, performed so many years after the investigations just described were made, have been able to confirm them in every detail.

In a paper by Dr. Whitehead and me (Morphology of the Gasserian Ganglion, *Brain* **48**:458, 1925) illustrations of the gasserian ganglion at an estimated age of 28 weeks are given, and the statement is made that "in the main" the peripheral divisions are represented in corresponding anatomic thirds of the sensory root. It is not denied that possibly the statement that the fibers of the sensory root do not tend to intermingle may need a certain modification, implied in the phrase "in the main." Between the age of 28 weeks and full term the complexity of the sensory root may increase.

In my paper in collaboration with Whitehead it is stated that the ganglion undergoes rotation, whereby its lateral surface finally becomes its dorsal surface. This observation is confirmed by Davis and Haven, and their statement that division of the lower part of the sensory root at its entrance into the pons will have the same result as division of the sensory root in the ophthalmic portion at its entrance into the gasserian ganglion, viz., keratitis and loss of the corneal reflex, justifies my technic, commonly spoken of as subtotal section with preservation of the ophthalmic portion. Davis and Haven refer to the recent contribution of van Nouhuys. In this he states that "the operation of partial section of the sensory root," as it is practiced in my clinic, "assuming that the pain is carried by bundles having a definite location, is not based on anatomic facts, and therefore cannot be regarded as an absolutely reliable procedure."

In refutation of this statement, I submit first the results of Davis and Haven's observation. To quote from Davis and Haven, "from these studies it is evident that, although there are no clearly defined funicular components in the sensory root at its entrance to the pons, and although there are numerous anastomoses along the course of the root, the fibers which form the various divisions of the gasserian ganglion appear to occupy a definite position in the root in the region of its entrance zone."

Finally, in refutation of van Nouhuy's statement, may I submit my personal clinical experience? Having performed this radical operation 731 times, I am convinced that after section of the outer third of the root alone there will be anesthesia only in the mandibular distribution; that if one sections the outer two thirds of the root there will be anesthesia in both the mandibular and the maxillary distribution; that if one leaves but two fasciculi of the opthalmic portion, sensation in the ophthalmic portion will be preserved, and there will be no corneal complications.

That Davis and Haven's observations support the principle of subtotal section by the temporal route and do not support that of partial section of the root at its entrance to the pons by the suboccipital entrance is a matter of grave importance. It has, I believe, been generally accepted that the suboccipital route is considerably more difficult and hazardous. The mortality, if this method were generally adopted, would necessarily be higher than when the temporal route is used.

Because we have been able to eliminate trophic keratitis, and because we have been able to reduce the hazards almost to zero (0.2 per cent) I maintain, contrary to van Nouhuy's statement, that subtotal section: (1) is based on anatomic facts; (2) is an absolutely reliable procedure, and (3) should continue to be recognized as the operation of choice.

I feel an obligation before this authoritative group of neurologists to present evidence in refutation of efforts made to discredit, by implication and otherwise, an operation which for the following reasons I have always called the Spiller operation: (1) because I was not familiar with the article in the *British Medical Journal* of December 12, 1891; (2) because Spiller, in 1898, unaware of Horsley's work in 1891, first proposed the operation to me; (3) because the first series of experimental operations to assure permanence of relief was carried out at the suggestion of Spiller; (4) because as late as 1897 Horsley implied that he had not repeated his operation on the sensory root and that he did not advise this operation for tic douloureux, as he stated that he regarded the Krause-Hartley operation as practiced in 1897 as the scientific operation for trigeminal neuralgia, and (5) because the repeated clinical experiences and contributions from the neurosurgical clinic of the University Hospital were largely, if not wholly, responsible for the acceptance of the operation on the sensory root throughout the world as a substitute for removal of the ganglion.

By the Spiller operation or by the temporal route operation, the motor root is conserved, trophic keratitis will not develop if the ophthalmic division is not disturbed, facial paralysis can be eliminated, and the results are permanent.

Dr. W. E. Dandy, Baltimore: Every surgeon has his own likes and dislikes concerning operative procedures. I adopted the suboccipital approach because I was having bad results with the subtemporal approach, and in Dr. Frazier's report published about the time my operation was introduced he said that the last word in trigeminal neuralgia had not been said, and that there were serious complications. It was to overcome these defects that the suboccipital approach was evolved.

Regarding the statement that the mortality is higher when the suboccipital approach is used, I need only say that in my last 150 cases there has not been a death, nor has there been a sequela of any kind. It is a perfectly safe procedure if used correctly, just as safe as the subtemporal approach. I think, and I think very strongly, that it gives superior results.

I have nothing to add to the original statement that I made in 1925 or 1926, that if approximately half of the sensory root is divided there will be slight sensory changes in the face. I accept Dr. Frazier's statement that he gets true anatomic distribution of the loss of sensation by partial sectioning. I do not know wherein lies the difference. I merely present results for what they are worth.

I made no statement that there was a rearrangement of fibers into bundles for each form of sensation. I said that there was some dissociation of sensation following partial section of the sensory root. There are frequently large areas in which heat and cold, for example, are lost, and touch is perfectly preserved. If there were an anatomic distribution of the nerves according to their peripheral divisions, that certainly would not hold.

It is not possible to transport results of this character from cats to human beings. Similar mistakes have been made many times in the past, for example, in determining the pathways for taste. Certainly there was no more competent and careful observer than Magendie, but it is impossible to determine on an animal the pathways for such sensations as taste and pain.

Furthermore, I am sure that a condition comparable to neuralgia of the trigeminal nerve has never been described in a cat, so that one is not justified in applying to human beings the observations made on cats.

Another similar misapplied observation was that on Goltz's dogs in which extirpation of the cerebral hemispheres caused no paralysis. The false security assumed in applying the results of this canine experiment to human beings withheld the acceptance of the doctrine of cerebral localization for many years.

There is an elaborate anastomosis of fibers in the sensory root all along its course. Whether that has anything to do with the difference in results of Dr. Frazier's operation and mine, I am not prepared to say.

DR. LOYAL DAVIS, Chicago: I want to emphasize again what Dr. Spiller has said about the dissociation of fibers in the sensory root as compared with that which occurs within the pons. Whereas it has been established definitely that fibers carrying painful impulses pass downward within the pons in the descending tract, there is no evidence that a grouping of fibers according to the sensation which they carry is present in the sensory root external to the pons.

We have shown, I think rather conclusively, from our degeneration experiments that when a section is made in the sensory root near the pons, in the same location as that described in Dr. Dandy's operative procedure, degeneration occurs in the ventral portion of the descending root of the fifth nerve. This picture of degeneration is exactly similar to that which occurs when the ophthalmic division is cut near the ganglion. This work is confirmatory of that of Spiller and van Gehuchten.

All of the patients with trigeminal neuralgia operated on by the suboccipital approach by many neurologic surgeons have shown a definite loss of all types of sensation over the distribution of the fifth nerve, depending on the amount of the sensory root which has been cut. While it is undoubtedly true that one should apply knowledge obtained from experiments on animals to the human being with some reservations, nevertheless both in animals and in man the function of a sensory nerve fiber is the same. Either in animals or in man, if one cuts a portion of a root containing sensory fibers one should expect a loss of sensation. At least to that extent we may apply such physiologic experiments.

As a result of our experiments in gross anatomy, on the basis of embryologic data and of histologic examination of the sensory root in animals and in man and as a result of degeneration experiments, not to mention the clinical material which is on record, we feel convinced that if one desires to perform a subtotal section of the sensory root of the trigeminal nerve in order to preserve certain fibers, it is more logical to make the section near the ganglion and, finally, that there is no evidence to support the view that section of the sensory root near the pons will relieve the pain of trigeminal neuralgia without producing a definite loss of sensation.

VARIATIONS IN SKIN ANESTHESIA FOLLOWING SUBTOTAL RESECTION OF THE POSTERIOR ROOT

WITH A REPORT OF TWENTY-SIX CASES ILLUSTRATING A SERIES OF VARIATIONS

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For the past twenty or twenty-five years, it has been accepted that the only positive way of curing a patient with a severe trigeminal neuralgia is by separating the connections between the gasserian ganglion and the central nervous system. The old procedure of Hartley and Krause of removing the gasserian ganglion has been superseded by section of the posterior root of the ganglion. This procedure, dividing the posterior ganglionic fibers, was first suggested and carried out by Sir Victor Horsley,[1] in 1891. His patient, however, was very feeble and died a few hours later. One of us (Dr. Sachs) in 1907 frequently saw Horsley carry out this procedure; he did not divide the root, but always extracted it from the pons. At that time he often pointed out that in some cases the ophthalmic fibers lay in a separated group in the mesial portion of the root, but in other cases there was no separation that could be seen between the fibers passing to the second and third divisions and those passing to the first division. This entire subject, from both the clinical and the anatomic aspect, was

Since this article was sent in for publication, an interesting anatomic study of the posterior root of the gasserian ganglion, by F. van Nouhuys, of Leiden, Holland, appeared in the March, 1932, issue of the Archives of Surgery (The Anatomy of the Gasserian Ganglion, p. 451). In this work, the author has found anatomic evidence of what our cases show clinically; namely, that there is interlacing of the fibers in the posterior root, especially of the ophthalmic and maxillary portions.

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1. Donald Armour (Brit. M. J. **2**:163 [July 25] 1931) has drawn attention to the fact that Horsley (Lectures at Queens Square, London, The Medical Publishing Company, 1897) suggested and carried out this procedure seven years before the appearance of the paper by Spiller on this subject.

studied exhaustively by Frazier and Spiller [2] and later still further by Frazier and Whitehead.[3] As a result of these studies, the operation of section of the posterior root was still more perfected. In 1917, Frazier preserved the motor root of the fifth nerve, thus preserving the function of the muscles of mastication and preventing their atrophy. Though in a unilateral trigeminal neuralgia the preservation of the motor root is not of such vital importance, it is absolutely essential for the occasional case of bilateral neuralgia.

The possibility of subtotal resection of the posterior root with preservation of the ophthalmic division was considered by Frazier for a number of years, but was first carried out by him in 1915. During the course of the next ten years, twenty-five cases were found that were considered suitable for this operation, and in all of these the patients had complete relief.[4]

In 1926, Frazier and Whitehead reported their studies on the development of the posterior root. They showed that fibers to the three divisions develop as separate bundles, and that the ophthalmic portion develops earlier than the other two portions. They found some intermingling of fibers of the second and third divisions and thought that this explained the frequent association of pain in the second and third divisions and the infrequency of involvement of the ophthalmic division, as it would be less vulnerable than the phylogenetically younger structures.

For some years it has been the rule in the clinic of the Washington University School of Medicine to try to preserve the ophthalmic portion of the posterior root in all suitable cases, that is, in those in which there is no pain in the distribution of the first division or in those in which the pain in the first division is so slight that it is believed to be a spread and not an actual involvement of the first division.

Whereas the ophthalmic fibers may lie as an entirely separate group, as pointed out by Horsley twenty-five years ago, in our experience in the vast majority of cases this does not occur, and, therefore, as there is no distinct line of cleavage, one must estimate which portion of the root contains the ophthalmic fibers. We have operated on some patients under local anesthesia, believing that we might identify more accurately

2. Frazier, C. H., and Spiller, W. G.: The Division of the Sensory Root of the Trigeminus for the Relief of Tic Douloureux: An Experimental, Pathological and Clinical Study, with a Preliminary Report of One Surgically Successful Case, Philadelphia M. J. **8**:1039 (Dec. 14) 1901; Physiological Extirpation of the Ganglion of Gasser, J. A. M. A. **43**:943 (Oct. 1) 1901.

3. Frazier, C. H., and Whitehead, Edward: Morphology of Gasserian Ganglion, Brain **48**:458 (Dec.) 1925.

4. Frazier, C. H.: Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **13**:378 (March) 1925.

the fibers to a certain root, but, as procaine hydrochloride must be injected into the root, this tends rather to confuse the picture than to clear it up (case 23). Most operations, therefore, have been done in the past two years, under tribromethanol, with procaine hydrochloride for the skin, and at times a very small amount of ether.[5]

After operation, every patient is carefully examined for pain, touch and temperature sensibility. The loss to pain is the most accurate field to map out, and it is this field that is recorded in the cases reported in this article.

Twenty-six cases are reported here, and they show such great variations in the sensory loss that we have felt it important to record them. They illustrate that even with the greatest care a fiber or a few fibers may be missed. Some of the cases also, we believe, indicate that there is considerable interlacing of the fibers, and that adjacent nerve fibers do not always supply adjacent areas of skin. The cases also indicate that there is some interlacing between the ophthalmic branch and the second and third branches.

The cases have been divided into four groups:

Group I: Three cases, in which the entire posterior root was supposed to have been removed.

Group II: Eleven cases, in which only the second and third divisions of the posterior root were divided.

Group III: Eight cases, of division of the second and third portions of the posterior root, in which the anesthesia does not show the usual "tongue-like" extension supplied by the third division in the temporal region.

Group IV: Four cases, in which the pain was confined to the third division and an attempt was made to divide only the fibers of the third division.

REPORT OF CASES: GROUP I

CASE 1.—*History.*—M. R., a white woman, aged 68, was admitted to the Barnes Hospital on Jan. 8, 1924, with typical trigeminal neuralgia of four years' duration. Pain was experienced in all three branches, but primarily in the second division. The chief complaint was of lancinating pain in the left side of the face, with onset four years prior to admission. The pain was primarily in the second division; there was a trigger zone just lateral to the nose on the left cheek and in the left nasal passage. Three injections of alcohol had given relief for from three to nine months each, but several injections after this gave no relief.

Physical Examination.—There were a Horner's syndrome on the left side, a widened area of dulness beneath the sternum, a moderate enlargement of the heart,

5. We have been reducing our dose of tribromethanol in the past year and now give from 80 to 90 mg. per kilogram of body weight, and, if the patient is not perfectly quiet, a little ether is given on an open mask. Usually a teaspoonful or two suffices.

a systolic murmur and a blood pressure of 250 systolic and 110 diastolic. The patient had a mild dyspnea and swelling of the ankles.

The pain was unbearable, and in spite of the symptoms of cardiovascular disease operation seemed imperative. Complete section of the posterior root was planned.

Operation (Dr. Sachs).—On Jan. 11, 1924, under ether anesthesia, the usual approach to the ganglion was used. The dura was adherent throughout the middle fossa. Considerable hemorrhage was encountered. The foramen spinosum was plugged with an orris root stick to control hemorrhage from the middle meningeal artery. Adhesions were encountered when the dura over the ganglion was incised. The fibers themselves were bound together, and very little cerebrospinal fluid escaped. The posterior root was cut. The entire sensory root was thought to have been removed, and the wound was closed in layers without drainage.

Fig. 1 (case 1).—The area supplied by the first division was absolutely intact, and apparently a few fibers belonging to the second division were also left.

Postoperative Course.—This was uneventful. Examination revealed that sensation of the forehead, eye and cornea was intact and acute (fig. 1).

CASE 2.—*History.*—L. R., a white man, aged 54, was admitted to the Barnes Hospital on Jan. 9, 1925, with typical neuralgia of the right fifth nerve, primarily involving the second division, of a duration of twelve years. The past and family history was irrelevant. The present illness began with a sudden onset, twelve years before, of typical severe lancinating pain in the right maxillary region, which tended to recur in paroxysmal attacks induced by talking, eating, washing the face and movement of the eyes to the right. Four years prior to admission, an injection of alcohol gave relief for a short time. Then all the teeth were extracted without relief. Recently the pain had spread to the forehead.

Physical Examination.—The patient was in good general physical condition. The pupils were sluggish in reaction; there were occasional facial spasm and some

lateral nystagmoid twitching, which suggested a lesion of the posterior fossa compressing the root of the fifth nerve. The motor fifth nerve and auditory nerve were uninvolved. The Wassermann reaction of the blood was positive.

Operation (Dr. Sachs).—On Jan. 12, 1925, under ether anesthesia, the usual approach to the ganglion was used. There was troublesome hemorrhage in the region of the middle meningeal artery. Instead of the usual small foramen spinosum, a large defect in the floor of the middle fossa was encountered. This was controlled by a cotton pack that was left in place. The posterior root was readily exposed, and all of the fibers were removed. They did not pull out from the pons as usual, but broke off. The wound was closed in layers without drainage.

Postoperative Course.—This was uneventful. Sensation in the area of the first division, including corneal sensitivity, remained intact (fig. 2).

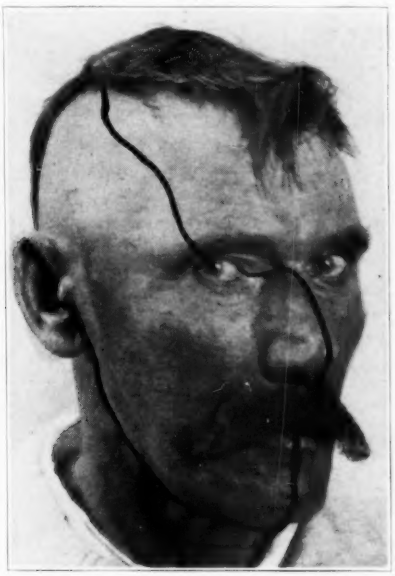

Fig. 2 (case 2).—Some of the first division fibers were removed as part of the area supplied by the first division remained sensitive.

CASE 3.—*History.*—C. M., a colored man, aged 32, was admitted to the Barnes Hospital on Aug. 17, 1927, with neuralgia of the right side of the face, primarily of the second division, of seven years' duration. The chief complaint was intermittent, severe, stabbing pain in the right side of the face for seven years. The illness began with the sudden onset of severe, shooting pain in the right temporal region; this had recurred intermittently up to the time of admission. The pain was precipitated by salty or sour substances and exposure to cold. In 1924, all the teeth were extracted without relief. An injection of alcohol was made in May, 1926, with relief for one week. A second injection, in September, gave relief for but one week.

Physical Examination.—The patient was well nourished and healthy, and presented no positive neurologic findings except a hypersensitivity of the skin over the right side of the face.

Operation (Dr. Klemme).—On Aug. 19, 1927, under ether anesthesia, the usual exposure of the ganglion was carried out. The foramen spinosum was plugged with an orris root stick. Considerable difficulty was experienced in exposing the ganglion. Everything was adherent about the root, and as the fibers were removed the motor root was also extracted. At the time of operation it appeared that all the fibers had been removed. Closure was made with the usual layers.

Postoperative Course.—This was smooth. Pain was relieved. The patient was discharged from the hospital two weeks later. A small area at the chin, to the right of the midline, remained sensitive (fig. 3).

Comment.—In case 1 the fibers of the first division were not removed, and it may be that in this case the ophthalmic fibers were in a separate trunk, but it is interesting that a few fibers on the inner side

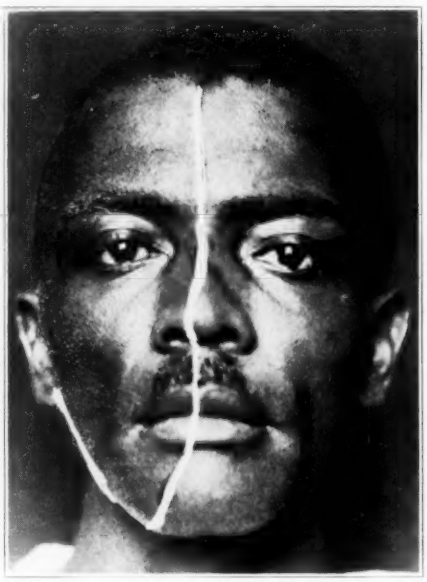

Fig. 3 (case 3).—A few fibers of the third division apparently were not removed.

of the root of the nose were also intact as this region is supplied by fibers from the second division.

In case 2 a considerable part of the fibers of the first division were removed, but those to the forehead remained. This patient had a return of pain, and three years later Dr. P. Bailey [6] reoperated on him and reopened the temporal wound. He had difficulty with hemorrhage and cut only the second division distal to the ganglion. When the patient's pain returned two years later, Dr. Bailey cut the fifth nerve in the posterior fossa and produced a complete anesthesia. One of us (Dr.

6. This case is no. 3 in Bailey's article (S. Clin. North America **11**:61 [Feb.] 1931).

Sachs) always questioned his diagnosis in this case and believes that this probably was not a true tic douloureux.

In case 3 there is a small triangular area on the point of the chin in which there is normal sensation. Either there were a few strands of the third division left, which is improbable, or there was an abnormal distribution and this small area was supplied by fibers from the opposite side.

GROUP II

CASE 4.—*History.*—G. H., a white man, aged 70, was admitted to the Barnes Hospital on Oct. 23, 1928, with typical trigeminal neuralgia involving all three divisions. He had had gastric discomfort at the age of 23, which had

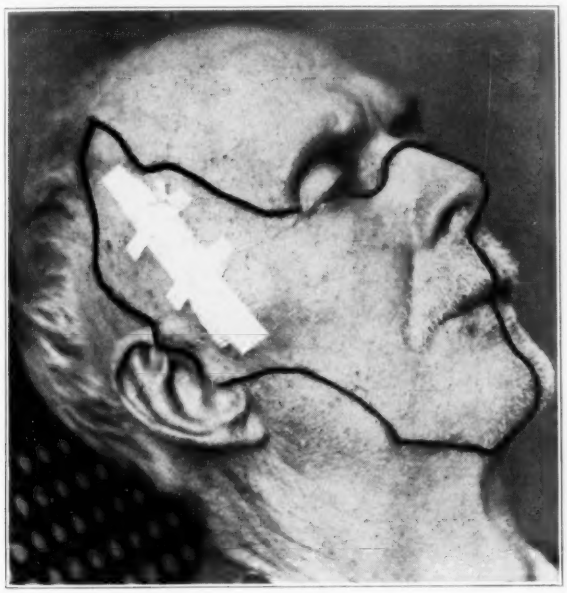

Fig. 4 (case 4).—As there is partial anesthesia of the areas supplied by both the first and second divisions, this case suggests interlacing of the fibers.

subsided. Herniotomy was performed in 1925, without complications. The pain began ten or twelve years prior to examination in the region of the right lower third molar. There was typical intermittent paroxysmal pain which was precipitated by shaving, washing of the face and eating. The patient's teeth were removed one after the other without relief. Three years later, the second division became involved, and more recently the pain had spread to the first division. One attempt at an injection of alcohol was unsuccessful.

Physical Examination.—The patient was rather slender but well preserved, with a moderate degree of arteriosclerosis and a blood pressure of 140 systolic and 70 diastolic. There was a "trigger zone" at the right infra-orbital foramen and in the right nostril. A subtotal resection of the posterior root was advised as the spread of pain to the forehead was recent.

Operation (Dr. Sachs).—On Oct. 24, 1928, the usual vertical incision in the temporal region was made. The middle meningeal was clipped with a silver clip and cut. The fibers of the first division were isolated. The fibers of the second and third divisions were pulled forward and cut with scissors. The wound was closed in layers.

Postoperative Course.—Recovery was smooth, and the patient was discharged from the hospital five days later. There had been no recurrence of pain. The distribution of the anesthesia was irregular; some of the fibers of the second division were left, and a portion of the fibers of the first division was removed (fig. 4).

CASE 5.—*History.*—J. D., a white man, aged 67, was admitted to the Barnes Hospital on March 19, 1928, with typical trigeminal neuralgia of the second and third divisions. His chief complaint was severe pain in the upper and lower

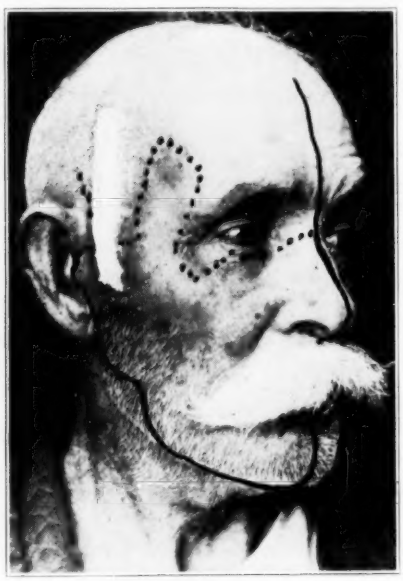

Fig. 5 (case 5).—As the anesthesia extends into the first division area, this also suggests the possibility of interlacing of the fibers.

jaws on the right. His mother had suffered from a similar pain but of less severity. His past history was irrelevant. The present illness began suddenly in October, 1924. The primary site was the maxillary region. All the teeth were extracted without relief. The pain then spread to the mandibular region. Eating, talking and extreme heat or cold precipitated an attack. The pain never crossed the midline. An injection of alcohol gave relief for seven months; a second injection gave relief for sixteen months. Operation was advised as the pain had recently returned and the patient wished for permanent relief.

Physical Examination.—The chest was emphysematous. The blood pressure was 140 systolic and 90 diastolic. The patient's general condition otherwise was excellent, and there were no positive neurologic signs. As the first division had never been involved, a differential section was indicated.

Operation (Dr. Sachs).—On March 21, 1928, under ether anesthesia, the usual vertical incision was made. After opening the bone, the patient's pulse became imperceptible, and the operation was stopped for a few minutes. Later in the operation, a similar thing occurred, but as the condition improved the operation was continued; the posterior root was exposed, and the ophthalmic group of fibers was identified. These fibers were preserved, and the others were extracted. The slight bleeding from the cavernous sinus was controlled by placing a bit of muscle over the bleeding point. The muscles were closed in layers without drainage.

Postoperative Course.—Recovery was uneventful. There was no recurrence of pain. There was anesthesia of the area supplied by the second and third divisions as shown in figure 5. The area of anesthesia, however, extended into the region of the first division.

Fig. 6 (case 6).—The peculiar area of normal sensation in the middle of the forehead indicates clearly that the fibers to this area could not have been lying next to the rest of the first division fibers.

CASE 6.—*History.*—I. M., a white woman, aged 55, was admitted to the Barnes Hospital on June 5, 1929, with typical trigeminal neuralgic pain, primarily of the third division. The chief complaint was of pain in the upper and lower jaws on the right side. The mother and two sisters had had pulmonary tuberculosis. The patient had had the usual diseases of childhood. She had had symptoms of tuberculosis at 23 years of age, but recovered completely.

The present illness began ten years prior to admission, with intermittent, sharp, shooting pains below the right eye. The pain was that of a typical neuralgia, and was intensified by extremes of temperature, but was always limited to the right side of the face. All the teeth were extracted without relief. A peripheral injection of alcohol at the mental foramen gave relief for six years. The pain recurred a year prior to examination, but at first was not severe, and an application of

ultraviolet rays and liniment relieved the pain. Severe pain recurred two months before examination and at the time of admission was "unbearable."

Physical Examination.—The patient was slender but apparently healthy. The only abnormal physical finding was a slight diminution of the sense of pain over the right side of the face; the blood pressure was 140 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. An injection of alcohol was advised, but the patient refused it as she desired permanent relief.

Operation (Dr. Sachs).—On June 7, 1929, a McKenzie incision was made, the anterior approach to the middle meningeal artery being used. The operator feared that the upper branches of the facial might be injured by this incision. The skull was opened in the usual way. The middle meningeal artery was coagulated with the Bovie unit and then cut. When the posterior root had been exposed, adhesions

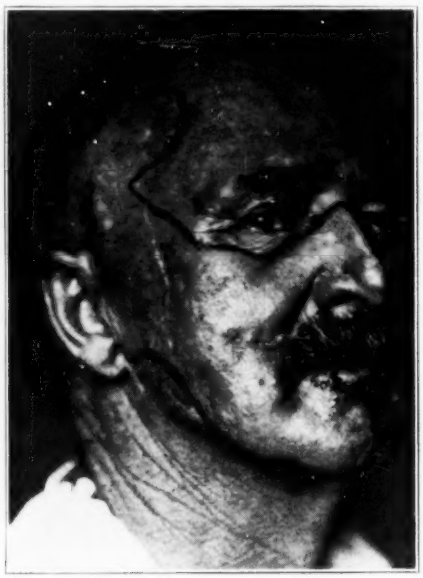

Fig. 7 (case 7).—The sensory loss is not confined to just the areas supplied by the second and third divisions.

were found between the dura and the root which made freeing of the root difficult. The ophthalmic fibers were left intact. The motor root was sacrificed. The wound was closed in layers.

Postoperative Course.—Recovery was uneventful. Sensory examination revealed that only the outer inferior quadrant of the cornea was sensitive. Tears continued to moisten the eyeball. A small area on the upper lid and on the forehead was normally sensitive. The remainder of the forehead was hypesthetic, and the lower part of the face was anesthetic. The upper branches of the facial nerve were injured, as evidenced by a flattening of the forehead on the right side.

Case 7.—*History.*—J. S., a white man, aged 65, was admitted to the Barnes Hospital on April 8, 1931, with typical trigeminal pain of eight years' duration. His chief complaint was of pain in the right side of the face. The family history was not significant. The patient had had precordial pain for eight or

nine years. He had had valvular disease with hypertension for two years. He had had gastric hemorrhages from an ulcer (?) five years previously.

The present illness began eight years prior to admission with pain on the right side. The pain was paroxysmal and burning in character. It began in the lower jaw and was precipitated by washing the face. Local applications were used without obtaining relief. The pain ceased spontaneousiy in 1928, but returned in August, 1930. The pain could be started by touching the upper lip. Between the attacks the patient complained of a deep ache in the "cheek bone."

Physical Examination.—The patient was well nourished and well developed; he was having frequent attacks of pain, at which times he showed the classic picture of a trigeminal neuralgia. The heart was enlarged, and the superficial vessels showed marked sclerosis. A soft blowing systolic murmur was heard at the apex. The blood pressure was 220 systolic and 90 diastolic. Hearing was diminished bilaterally—catarrhal deafness. The patient had right inguinal hernia that was easily reducible. Renal function was good, 75 per cent phenolsulphonphthalein in two hours. The urine showed a trace of albumin. The Wassermann reaction of the blood was negative. Because of the hypertension, a local anesthetic was thought advisable.

Operation (Dr. Klemme).—On April 9, 1931, under local anesthesia, the usual approach was employed. The middle meningeal artery was cut after ligation with silk. Procaine hydrochloride was injected into the third division, and the dissection was carried back to expose the posterior root. The lower outer three fourths of the fibers were isolated and removed. The wound was closed, but a drain was inserted because of the high blood pressure and the possibility of oozing. The systolic blood pressure fell from 200 to 90 during the operation, but the patient's condition was excellent.

Postoperative Course.—Recovery was uneventful except for a rather sharp rise in temperature on the second day. The pain was relieved, and the patient was discharged on the sixth day. The sensory loss is shown in figure 7.

CASE 8.—*History.*—J. W., a white man, aged 68, was admitted to the Barnes Hospital on Nov. 17, 1930, with typical attacks of trigeminal pain. His chief complaint was of paroxysmal attacks of pain in the right side of the face and deafness. His grandfather died of a "stroke"; his father suffered from pain similar to that of the patient. The past history of the patient was irrelevant. The patient had had momentary attacks of severe burning pain in the right side of the lower jaw for the past six years. Exposure to cold wind and very hot or very cold food precipitated the attacks. All of the patient's teeth were extracted without relief. The pain had gradually increased in severity until two years prior to admission, when it ceased spontaneously. Six weeks before admission, the pain recurred and had since been practically unbearable. In the interval between the attacks the patient complained of a constant ache and soreness.

Physical Examination.—The patient presented the classic picture of a trigeminal neuralgia. In addition, he had a marked decrease in hearing bilaterally, lateral nystagmoid twitchings and a decrease in the olfactory sensation. His general condition was excellent for his age. In spite of the presence of these other signs, the pain was typical and severe, indicating resection of the posterior root. The Wassermann reaction of the blood was positive.

Operation (Dr. Sachs).—On Nov. 18, 1930, under tribromethanol and local anesthesia, the middle meningeal artery was exposed and clipped with a silver clip. The posterior root was then exposed and an arbitrary division of fibers made,

approximately the lower outer two thirds of the posterior root being removed. The usual closure in layers was made.

Postoperative Course.—Recovery was uneventful. Unusually severe herpes developed. The sensory findings are shown in figure 8.

Case 9.—*History.*—H. T. S., a white man, aged 53, was admitted to the Barnes Hospital on July 10, 1930, with typical trigeminal neuralgia of the right side. His chief complaint was of paroxysmal pain in the right side of the face of seven years' duration. The family and past history was irrelevant. The present illness began with the sudden onset of a typical lancinating pain, which occurred from four to five times daily and recurred every three or four weeks. The pain always began in the maxillary region. Shaving, eating or even touching the upper lip precipitated an attack. The pain sometimes spread to the eye. Sev-

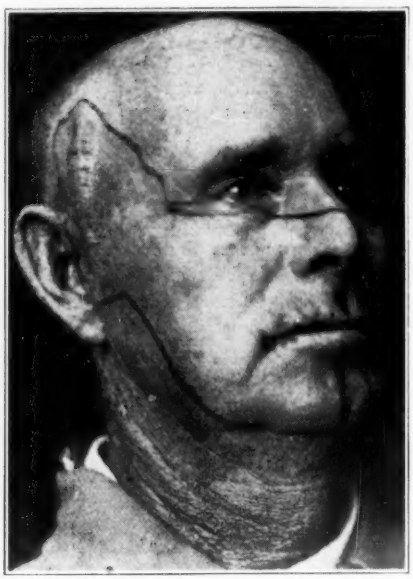

Fig. 8 (case 8).—Here again, the sensory loss is not confined to just the areas supplied by the second and third divisions.

eral injections of alcohol had given transient relief or none at all. Extraction of all the teeth also failed to give any relief. The infra-orbital nerve had been cut, but the pain had continued.

Physical Examination.—The patient was well developed and slender, and had a moderate degree of peripheral arteriosclerosis but a low blood pressure, 105 systolic and 65 diastolic. The urine contained a trace of albumin; a phenolsulphonphthalein test gave 55 per cent in two hours. The Kahn reaction of the blood was negative. The patient was advised to have an injection of alcohol, but this he refused.

Operation (Dr. Sachs).—On July 12, 1930, under tribromethanol anesthesia, with local infiltration with procaine hydrochloride, the patient became excited and unmanageable; he was anesthetized with ether. The middle meningeal artery was exposed, coagulated and cut. The posterior root was exposed. As there was no

line of demarcation, a generous bundle of fibers to the first division was left intact. The closure was in layers without drainage.

Postoperative Course.—Recovery was uneventful, except for a right facial paresis that appeared twenty-four hours after the operation. This cleared up in a short time. All the fibers of the first division and a portion of those of the second division remained intact (fig. 9).

CASE 10.—*History.*—I. R., a white woman, aged 46, was admitted to the Barnes Hospital on April 9, 1931, with trigeminal pain, primarily in the maxillary division. The family and past history was irrelevant. The present illness began in 1927 with typical paroxysmal attacks. The pain was primarily in the second division; it was always limited to the distribution of the right fifth nerve. Sometimes it occurred when the patient was asleep, causing her to awaken sud-

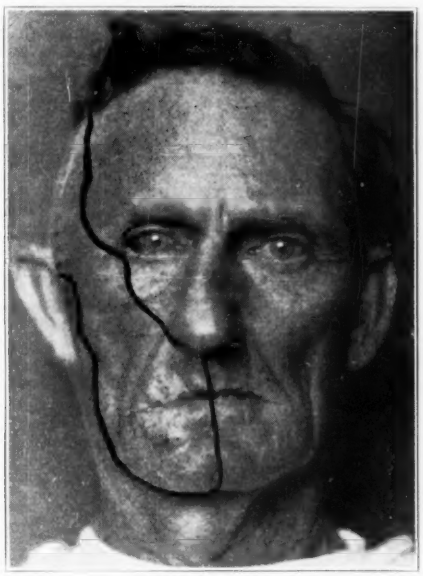

Fig. 9 (case 9).—This illustrates the impossibility at times of isolating the ophthalmic fibers from the rest of the root.

denly. An injection of alcohol in 1929 gave relief for nine months, and another in 1930 gave relief for seven months.

Physical Examination.—The patient was poorly nourished and offered little resistance to pain or illness; she enjoyed the attentions of the nurse or members of her family. Her chest and heart were normal. The blood pressure was 110 systolic and 70 diastolic. The patient kept the right side of the face "splinted" when she talked, to prevent pain. The tendon reflexes were hypo-active. A subtotal resection of the posterior root was advised.

Operation (Dr. Klemme).—On April 10, 1931, under tribromethanol and local anesthesia, the usual approach to the ganglion was employed. The middle meningeal artery was ligated and cut. The posterior root was exposed, and approximately the lower outer three fourths of the root were isolated and cut. Closure was made in layers without drainage.

Postoperative Course.—Recovery was uneventful. The patient was discharged from the hospital on the sixth day. The first division remained intact, and a few fibers, giving hypesthesia over the right side of the nose, remained (fig. 10).

CASE 11.—*History.*—E. H., a white woman, aged 47, was admitted to the Barnes Hospital on March 28, 1929, with trigeminal pain in the left mandibular division. The family and past history was irrelevant. The present illness began seventeen years prior to admission with typical attacks of pain, beginning in the third division on the left side. Pain was precipitated by washing the face; the pain was so severe that milk had been the only article of diet for some time. The teeth were extracted without relief. Various manipulative and electrical therapeutic measures were also tried, without relief. One injection of alcohol was given peripherally and gave relief for two years. The patient then desired permanent relief.

Fig. 10 (case 10).—Here also it was apparently impossible to separate only the first division fibers.

Physical Examination.—The patient was well developed and well nourished. The lungs and heart were normal. There was a "trigger zone" about the left angle of the mouth and also one on the inner wall of the cheek. The Wassermann reaction of the blood was negative; other laboratory tests gave normal results. Subtotal resection of the root was thought advisable.

Operation (Dr. Sachs).—On March 29, 1929, under ether anesthesia, the usual approach to the ganglion was made. The middle meningeal artery was unusually large and was cut after it had been ligated with silk. The posterior root was exposed, and what were judged to be the fibers to the second and the third divisions were isolated and sectioned. Closure was made in layers without drainage.

Postoperative Course.—Recovery was uneventful. The patient was discharged from the hospital on the seventh day. Sensation of the entire first division was retained, and a portion in the maxillary region only was hypesthetic (fig. 11).

CASE 12.—*History.*—J. S., a white man, aged 47, was admitted to the Barnes Hospital on Jan. 22, 1931, with typical trigeminal neuralgia, primarily in the right second division. His chief complaint was of "pain in the right cheek." The family history was irrelevant. The patient had experienced a trauma to the left mastoid in 1909; this was followed a year later by mastoiditis. A mastoidectomy was done; there was drainage of pus intermittently from the left ear, which resulted in deafness on that side.

The present illness began with typical, sharp, shooting pain in the upper jaw on the right side. The pain was brought on by talking, eating or any movement of that side of the face or blowing the nose. The pain had been present for eighteen months. The attacks of pain had been more frequent in the past few weeks. Two injections of alcohol were attempted, but neither relieved the patient.

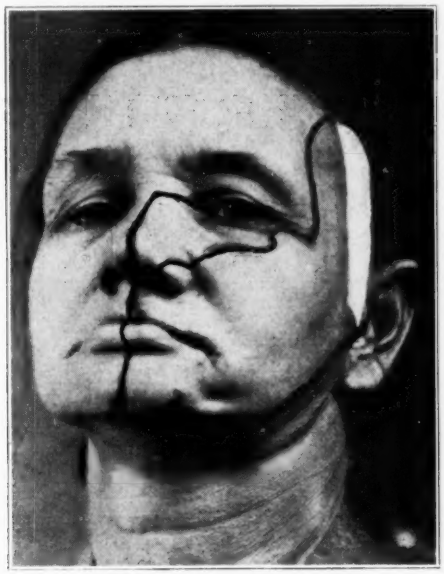

Fig. 11 (case 11).—The fact that part of the area supplied by the second division was only hypesthetic indicates that it takes more than one group of fibers to produce complete anesthesia over an area.

Physical Examination.—The patient was well developed and well nourished. There was an old mastoid wound on the left side. The patient heard nothing with that ear. There was hypesthesia of the second division of the right fifth nerve. As the pain had not been relieved with injections of alcohol, resection of the posterior root was advised.

Operation (Dr. Klemme).—On Jan. 23, 1931, under tribromethanol and local anesthesia, the usual approach to the ganglion was followed. The middle meningeal artery was torn, and the foramen spinosum was plugged with an orris root stick to control the hemorrhage. The third division of the fifth nerve was exposed, and alcohol was injected. The posterior root was then exposed, and the outer inferior two thirds were isolated and cut. The motor root was uninjured. Closure was made in layers.

Postoperative Course.—Recovery was satisfactory. A small area above and lateral to the mouth remained sensitive. The skin over the right side of the nose was hypesthetic, but there were areas supplied by the first division which were anesthetic (fig. 12).

CASE 13.—*History.*—I. G., a white man, aged 48, a priest, was admitted to the Barnes Hospital on April 7, 1931, with typical trigeminal pain, primarily of the second division. His chief complaint was of paroxysmal pain in the right side of the face. The family history and past history was irrelevant. The present illness began suddenly, seven years previous to admission, with severe pain in the right maxillary region. Talking, eating and extreme cold precipitated the attacks. The patient had had injections of alcohol on several occasions. On one occasion he had had relief for eight months. At the time of admission the pain now radiated to the forehead, in addition to shooting into the upper jaw.

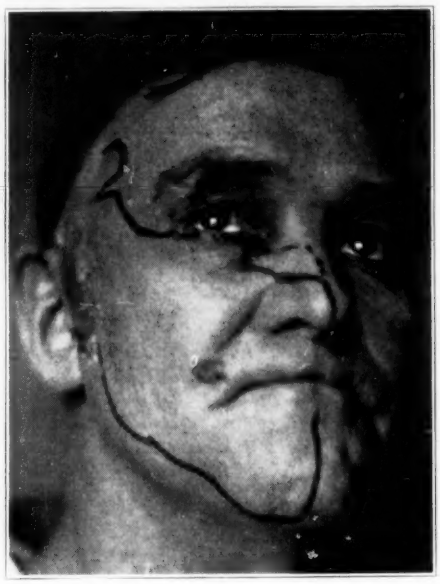

Fig. 12 (case 12).—This indicates clearly that there is a crossing of the fibers in the posterior root.

Physical Examination.—The patient was in excellent physical condition. The lungs were clear, and the heart was normal. There was a seborrheic dermatitis over the right side of the face. There was mild hypesthesia of the second and third divisions of the fifth nerve on the right side. A subtotal resection of the posterior root was advised.

Operation (Dr. Sachs).—On April 8, 1931, under tribromethanol and local anesthesia, with a preliminary dose of morphine, ⅙ grain (0.01 Gm.), the usual approach via the middle fossa was followed. The middle meningeal artery was exposed and coagulated. The presence of adhesions caused some delay as the ganglion was lifted out of its bed. The posterior root, when exposed, was found flattened out. The fibers supplying the second and third divisions were identified and removed. The motor root was undisturbed. The closure was in layers without drainage.

Postoperative Course.—Recovery was uneventful. There was complete relief from pain. All the area of the third division was anesthetic, while the area supplied by the second division was hypesthetic (fig. 13).

CASE 14.—*History.*—L. K., a white woman, aged 34, was admitted to the Barnes Hospital on May 21, 1931, with trigeminal neuralgia of the second and third divisions. Her chief complaint was of paroxysmal pain in the right side of the face. The mother had died of cancer of the face. A sister died of meningitis or a tumor of the brain. The past history of the patient was irrelevant. The present illness began in May, 1929, with severe pain in the right side of the tongue. It soon spread to the lower jaw. Trichlorethylene gave relief for a year. The patient was then free from pain from July, 1930, to February, 1931. Recently, the pain had returned and had been unbearable. The inferior alveolar nerve was evulsed without relief. Superficial injections into the supra-orbital and infra-orbital

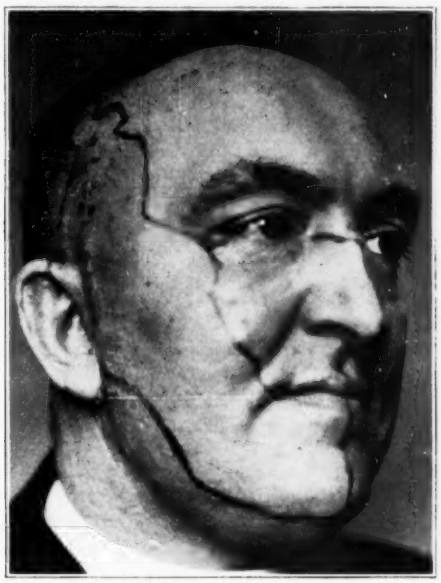

Fig. 13 (case 13).—This indicates, as in figure 11, that there is a variation in the depth of anesthesia, depending on how many fibers are left intact.

nerves did not stop the pain. The pain started on the posterior part of the tongue and extended upward to the temporal region.

Physical Examination.—The patient was well developed and moderately well nourished, but was more or less demoralized by the repeated attacks of pain in the right side of the face. The blood pressure was 118 systolic and 70 diastolic. There was an unhealed operative wound above the inferior canine tooth on the right side of the upper jaw. There were small areas of hypesthesia, one above the orbit and the other in the region of the mental foramen.

Operation (Dr. Sachs).—On May 25, 1931, under tribromethanol and local anesthesia, the usual temporal approach was made. The field was practically bloodless. A clip was applied to the middle meningeal artery, and it was then cut. A line of cleavage was easily found separating the second and third divisions from

the first. These were cut after procaine hydrochloride had been injected into them. As the portion left seemed too large for the ophthalmic portion, a few more fibers were removed. The usual closure in layers was made.

Postoperative Course.—Recovery was complicated by a complete facial paralysis, which appeared on the second day, and also by tinnitus with vertigo which, however, had cleared up by the seventh day. Figure 14 shows the sensory findings.

Comment.—The varied sensory findings in this group are extraordinarily interesting. They indicate undoubtedly that there are crossing and interlacing of the fibers in the posterior root. In this group, the most puzzling cases are cases 6, 10, 11, 12 and 14.

Fig. 14 (case 14).—The same point as is shown in figures 11 and 13 is illustrated.

In case 6 the two patches of normal sensation, one on the outer portion of the eyelid and one in a small area on the forehead, and the small patch of sensation in case 12, just above the outer corner of the mouth, are particularly interesting. They seem to justify the conclusion that the separate fibers in the posterior root supply distinct areas of the face and that the fibers to adjacent areas of skin do not necessarily lie next to one another in the posterior root. Cases 10 to 14, in which there is partial loss of sensation of portions of the area supplied by the second division, indicate that there is a certain amount of overlapping, such as occurs in other peripheral nerves, so that if some fibers are left only a partial loss of sensation occurs.

GROUP III

CASE 15.—*History.*—C. K., a white man, aged 55, was admitted to the Barnes Hospital on March 3, 1929, with trigeminal neuralgia, primarily in the second division, with a spread to the first and third divisions. The family and past history was irrelevant. The present illness began with pain in the right infra-orbital region. The pain spread rapidly; within a month it had spread to the forehead. All the upper teeth were extracted without relief. Alcohol was injected into the infra-orbital and supra-orbital nerves without relief. Six months before admission, the infra-orbital and supra-orbital nerves had been evulsed without relief. The pain had never spread to the opposite side.

Fig. 15 (case 15).—Since the fibers in the posterior root do not run parallel, it is useless to attempt to pick out the second division fibers.

Physical Examination.—The patient was poorly nourished and did not appear to suffer as much as these patients usually do. There was some anesthesia of the second division, but he continued to complain of pain. Several subcutaneous nodules over the head suggested von Recklinghausen's disease. The heart and lungs were clear. The blood pressure was 140 systolic and 80 diastolic. The Kahn reaction of the blood was 2 plus.

An injection of alcohol into the second division was first done, and we appeared to have a perfect "hit," but the pain was not relieved. Operation was requested by the patient.

Operation (Dr. Sachs).—On March 6, 1929, under ether anesthesia, the usual approach was made to the ganglion. The foramen spinosum was plugged with an orris root stick to control hemorrhage from the middle meningeal artery. The posterior root was exposed, and an attempt was made to isolate the second division

fibers as described by Stookey. These were cut, leaving the ophthalmic fibers and a few fibers of the third division intact. Closure was made in layers, with drainage, as considerable oozing had been encountered.

Postoperative Course.—Recovery was uneventful, except for the appearance of a transient facial weakness. The result was excellent as to anesthesia, but the patient complained of some pain below the right eye (fig. 15). The fibers of the third division were destroyed in this case. Undoubtedly the suggestion of taking only fibers of the second division is impracticable.

Case 16.—*History.*—J. T., a white man, aged 50, was admitted to the Barnes Hospital on May 6, 1929, with typical trigeminal neuralgia, primarily in the third division, but spreading to the second and first divisions. The family and past history was irrelevant. The present illness began four years prior to admis-

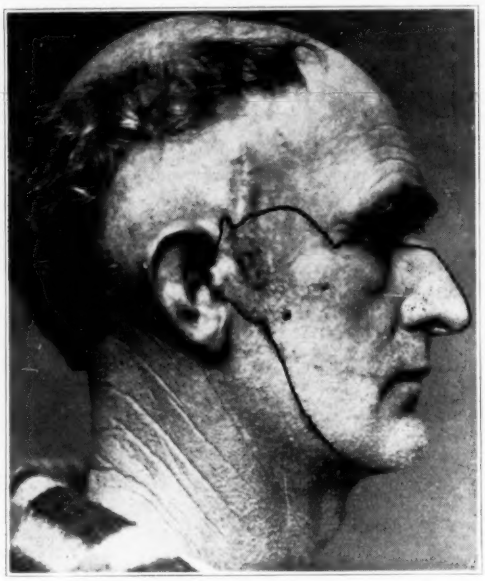

Fig. 16 (case 16).—This photograph illustrates the interlacing of the fibers of all three divisions.

sion, with typical trigeminal pain in the lower jaw on the right side. Eating, talking, washing the face and shaving precipitated the attacks. The pain spread to the maxillary region and more recently to the forehead, but always was limited to the distribution of the fifth nerve. Roentgen examination of the teeth gave negative results. The patient sought permanent relief and refused temporizing with injections of alcohol.

Physical Examination.—The patient was moderately well nourished and showed marked hyperesthesia over the right side of the face. There was a "trigger zone" at the angle of the mouth. The general condition was excellent except for moderate emphysema and enlargement of the prostate gland.

Operation (Dr. Klemme).—On May 7, 1929, under local anesthesia, the usual approach to the ganglion was followed. The middle meningeal artery was cut after ligating it with silk. An injection was made into the third division to decrease

the pain. The posterior root was exposed. The ophthalmic fibers were found as a separate isolated bundle. The remainder of the root was elevated and cut with scissors. Touching the fibers that were left produced pain in the region of the eye. Closure was made in layers without drainage.

Postoperative Course.—Recovery was uneventful. The patient was released from the hospital on the seventh day (fig. 16).

CASE 17.—*History.*—M. M., a white woman, aged 62, was admitted to the Barnes Hospital on Sept. 19, 1929, with trigeminal neuralgia, primarily in the maxillary region, with spread to the forehead and lower jaw. Her chief complaint was of pain over the left side of the face. The family history was irrelevant. The patient had had a mammectomy nine years before for questionable cancer of the breast. Hysterectomy had been done six months later for a fibroid. Recently she had had "chills and fever" which were relieved by quinine.

The present illness began twenty-five years previous to admission with typical pain in the second division. There were remissions that lasted for from two to

Fig. 17 (case 17).—It was only by careful sensory examination that this small area of normal sensation, owing to missing a few fibers of the second division, was demonstrated.

three years. Later, the pain spread to the lower jaw. For the past five months the pain had spread into the forehead. Extraction of teeth and a variety of medicines failed to relieve the pain.

Physical Examination.—The patient was intelligent and well preserved, and appeared to be in good health. The chest and heart were normal. There was a scar from an operation for the removal of the breast, and there were enlarged firm lymph nodes in each axilla. There was moderate hypertrophic arthritis. There was a small hypesthetic area on the upper lip. The patient preferred the operation for permanent relief of pain to the temporizing procedure of injections of alcohol.

Operation (Dr. Klemme).—On Sept. 20, 1929, under local anesthesia, the usual exposure was made of the middle fossa. Procaine hydrochloride was injected about the middle meningeal artery. The artery was ligated with silk and cut. Procaine hydrochloride was injected into the third division. The posterior root was exposed, and the greater part of the sensory root was cut, leaving a few fibers to the ophthalmic division. Stimulation of these fibers produced pain over the forehead.

Postoperative Course.—Recovery was uneventful. There was almost complete anesthesia of the maxillary and mandibular divisions; a small area of fairly normal sensation was left on the lower lid (fig. 17).

CASE 18.—*History.*—C. W., a white woman, aged 80, was admitted to the Barnes Hospital on May 7, 1930, with typical trigeminal neuralgia, primarily of the second division. The family history was irrelevant. The patient had had poor vision in the left eye for many years.

The present illness began twenty years prior to admission, with typical pain in the right maxillary division. Attacks recurred at varying intervals. They were precipitated by exposure to cold or washing the face. There were two "trigger zones," one anterior to the lobe of the ear and another on the side of the nose. In the past year the pain had become so intolerable that the patient insisted on relief by operation.

Fig. 18 (case 18).—Sensory disturbance following what was considered a satisfactory differential section.

Operation (Dr. Klemme).—On May 9, 1930, under local anesthesia, the usual approach was made. The middle meningeal artery was ligated with silk. Procaine hydrochloride was injected into the third division, and the posterior root was exposed. The outer inferior two thirds of the fibers were isolated and cut. Closure was made in layers.

Postoperative Course.—Recovery was entirely uneventful. There was an excellent result as to differential section of the nerve (fig. 18).

CASE 19.—*History.*—E. B., a white man, aged 80, was admitted to the Barnes Hospital on Aug. 21, 1928, with typical trigeminal neuralgia, primarily of the third division. The family and past history was irrelevant. The present illness began twenty-three years before admission, with typical neuralgic pain in the left side of the lower jaw. Peripheral extraction of the mental nerve gave relief for twenty-two years. One year prior to admission, the pain returned. Eight

months prior to admission, the patient began to have a similar pain on the opposite side, which spread into the area supplied by the first division.

Physical Examination.—The patient was emaciated, but appeared to be healthy. The chest was clear, and the heart was normal. The blood pressure was 160 systolic and 90 diastolic. There was bilateral impairment of hearing. Subtotal resection of the left side was advised. In case pain continued on the right, that side could be operated on later.

Operation (Dr. Klemme).—On Aug. 22, 1928, the usual approach was made. The middle meningeal artery was ligated with silk. The posterior root was split to preserve the ophthalmic division. The remainder of the fibers were then cut, and the motor root was left intact. Closure was made with the usual layers.

Postoperative Course.—The course in the hospital was excellent. Figure 19 shows the sensory loss.

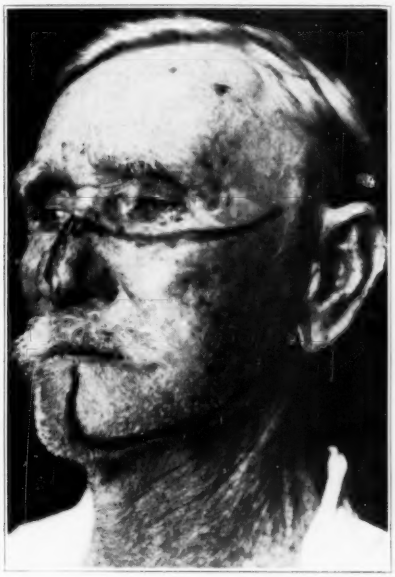

Fig. 19 (case 19).—Sensory disturbance following what was considered a satisfactory differential section.

CASE 20.—*History.*—P. K., a white woman, aged 41, was admitted to the Barnes Hospital on Oct. 10, 1928, with trigeminal neuralgia of the second and third division. The father had died one year before with questionable syphilis. The patient had been married for eighteen years, but had had no pregnancies.

The present illness began four years before admission, with typical paroxysmal attacks of pain in the second and third divisions on the right side. Exposure to cold and both liquids and solid food precipitated the attacks. In 1924, she had relief for twenty-eight days after an injection of alcohol.

Physical Examination.—The patient was well developed and well nourished. The heart was of normal size, but a systolic murmur was present. The blood pressure was 122 systolic and 96 diastolic. The Wassermann reaction of the blood was positive.

In spite of the positive Wassermann reaction, resection of the posterior root was thought advisable, as the pain was so typical and of such severity.

Operation (Dr. Klemme).—On Oct. 12, 1928, under ether anesthesia, the middle meningeal artery was tied with silk and cut. The posterior root was then exposed, and a little more than the outer half was removed. Closure was made with the usual layers.

Postoperative Course.—The course was complicated by a weakness of the seventh nerve, which appeared on the second postoperative day. The area supplied by the third division was totally anesthetic. Some fibers of the second division, however, remained, as the patient had only hypesthesia over the nose (fig. 20). She was referred to her family physican for intensive antisyphilitic treatment. The facial paralysis promptly cleared up.

CASE 21.—*History.*—E. D. B., a white woman, aged 67, was admitted to the Barnes Hospital on March 14, 1929, with trigeminal neuralgia, primarily of the third division. The family history was irrelevant. The patient had had a parkin-

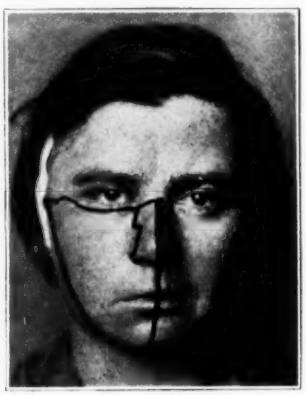

Fig. 20 (case 20).—Illustrating again the impossibility of isolating ophthalmic fibers completely. Such a result might also be explained by the interlacing of fibers.

sonian syndrome for several years. Fracture of the right hip occurred in an automobile accident in October, 1928.

The present illness began ten years prior to admission, with pain in the left side of the lower jaw. The pain was not very severe until one year before admission. There was a "trigger zone" on the left side of the tongue and on the lower lip. An injection of alcohol, made the previous fall, had given relief until recently.

Physical Examination.—The patient's general physical condition was good. She had an occasional extrasystole and moderate peripheral arteriosclerosis, with a blood pressure of 184 systolic and 100 diastolic. She had moderate limitation of motion in the right hip joint due to a fracture. The patient desired permanent relief.

Operation (Dr. Klemme).—On March 16, 1929, under ether anesthesia, the usual approach was made to the ganglion. The middle meningeal artery was not located; there seemed to be no foramen spinosum. The posterior root was exposed, and the lower outer two-thirds were isolated and cut. The motor root was undisturbed. Closure was made with the usual layers.

Postoperative Course.—Recovery was uneventful. The patient was discharged on the seventh day (fig. 21).

CASE 22.—*History.*—E. S., a white woman, aged 69, was admitted to the Barnes Hospital on Jan. 7, 1930, with trigeminal neuralgia, primarily of the third division, but spreading into the second. The family history was irrelevant with the exception that one brother has epilepsy. The patient had a chronic nonproductive cough; she had had pneumonia three times and some cardiac symptoms that respond readily to medication.

The present illness began six years before admission, with a dull aching pain over the left side of the chin, radiating to the angle of the jaw. Drinking, swallowing or touching the tongue to the lower lip precipitated the pain. At the time of admission the pain tended to spread into the second division. An injection of alcohol into the mental nerve gave relief for three weeks. Heat tended to lessen the pain for a time. Another injection of alcohol failed to give any relief.

Fig. 21 (case 21).—Sensory findings after leaving what were considered the ophthalmic fibers.

Physical Examination.—The patient was well nourished. The heart was moderately enlarged; a systolic murmur was present. The blood pressure was 210 systolic and 90 diastolic. The Wassermann reaction of the blood was negative. A faint trace of albumin was present in the urine, with an occasional hyaline cast.

As the pain was primarily in the third division, a subtotal resection of the root was advised, under local anesthesia because of the cardiac condition.

Operation (Dr. Klemme).—On Jan. 9, 1930, under local anesthesia, the usual approach was made to the ganglion. Considerable difficulty was experienced in elevating the dura because of adhesions. The middle meningeal artery was ligated and cut. The posterior root was exposed, and the fibers appearing to make up the ophthalmic division were saved. Closure was made with the usual layers.

Postoperative Course.—Recovery was complicated by mild postoperative shock and an annoying cardiac irregularity over a period of several days. The pain was completely relieved (fig. 22).

Comment.—This group illustrates the variations in sensory loss after what was a complete division of the portion of the posterior root containing the fibers to the third division. Most anatomic descriptions claim that there is a "tongue-like" process extending up in front of the ear, but in all these cases this was absent. Whether this "tongue-like" process is supplied by fibers from the second division might well be considered, since in a number of cases not all the fibers of the second division were cut.

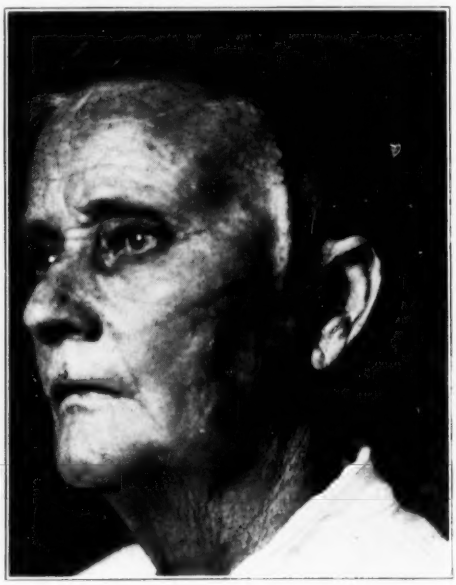

Fig. 22 (case 22).—Sensory findings after leaving what were considered the ophthalmic fibers.

The bizarre sensory disturbances in case 16 and especially in case 20 are further evidence, we believe, that it is not always possible to cut all the fibers that supply the second and third divisions and yet leave all ophthalmic fibers intact.

GROUP IV

CASE 23.—*History.*—Z. Q., a white woman, aged 47, was admitted to the Barnes Hospital on Dec. 10, 1929, with typical trigeminal neuralgia, primarily in the third division. A paternal uncle had suffered from a similar pain. The patient had been married for twenty-five years; there were no children; two pregnancies had been interrupted at 1 month; the cause was unknown.

The present illness began eight years before admission, with pain in the lower jaw on the right side, similar to a toothache. Soon this pain became typically lightning-like; exposure to cold wind, eating or washing the face would precipitate an attack. One attack lasted for four hours without cessation. An injection of alcohol had given relief for eleven months. The pain returned gradually and at the time of admission was very intense.

Physical Examination.—The patient was well developed and slightly obese, but appeared to have good health. The lungs were clear. The heart was normal. The blood pressure was 135 systolic and 100 diastolic. The patient tended to splint the right side of the face, and had a slight hypesthesia in the distribution of the second division. Radical operation was advised.

Operation (Dr. Sachs).—On Dec. 14, 1930, under local anesthesia, the usual approach to the ganglion was employed. In spite of the injection of procaine

Fig. 23 (case 23).—Indicating the impossibility of being certain of isolating all the second and third division fibers.

hydrochloride about the middle meningeal artery, severe pain was experienced when it was coagulated. An injection was made into the third division, and the posterior root was exposed. Manipulation produced such a severe pain that more procaine hydrochloride was injected. This gave such a widespread anesthesia that the anesthetist's reports misled the operator, as fibers were left that should have been cut. The patient was nauseated and vomited. Closure was made with the usual layers.

Postoperative Course.—Recovery was uneventful. At the end of the operation the entire second and third divisions were anesthetic. When the effects of the procaine hydrochloride had worn off, only the fibers of the third division and a few of those of the second division were found to have been cut (fig. 23).

CASE 24.—*History.*—G. W. S., a white man, aged 67, was admitted to the Barnes Hospital on March 10, 1929, with typical trigeminal neuralgia, primarily of the third division. The family history was irrelevant. The patient had had a carcinoma of the lip which had been removed with "cancer paste."

The present illness began fifteen months prior to admission, with typical lightning-like pain in the lower jaw on the right side. A few remaining teeth were removed without giving relief. The paroxysms of pain were more severe in the afternoon, and smoking tended to relieve the pain. In November, 1928, the patient had received an injection of alcohol, which gave relief for three months. Since then the pain had been very severe.

Physical Examination.—The patient was thin but well developed; his general condition was in keeping with his age. There was moderate peripheral arteriosclerosis. The blood pressure was 130 systolic and 82 diastolic. As the injection

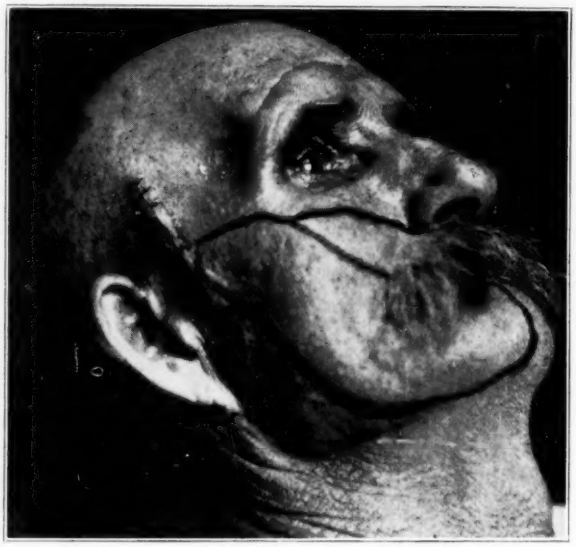

Fig. 24 (case 24).—Another instance of the same point shown in figure 23.

of alcohol had given relief for a comparatively short time, a subtotal resection of the posterior root was recommended.

Operation (Dr. Klemme).—On March 30, 1929, under local anesthesia, the usual exposure was made. The dura was adherent everywhere. The middle meningeal artery was ligated with silk and cut. The posterior root was then exposed, and the outer inferior two-thirds were cut. Closure was made in the usual manner.

Postoperative Course.—The course was complicated by a slight left hemiparesis, which appeared on the first day. This gradually cleared and had disappeared at the time of discharge. Pain was relieved. The upper portion of the second division was hypesthetic; evidently a few of the fibers of the second division were not cut (fig. 24).

CASE 25.—*History.*—L. W., a white woman, aged 49, was admitted to the Barnes Hospital on April 6, 1931, with typical trigeminal neuralgia, primarily of the third division. The family history was irrelevant. The patient's past history

was unimportant, except for a strangulated femoral hernia for which she had had performed an entero-enterostomy with repair and complete recovery after a stormy convalescence.

The present illness began nine years before admission, with typical pain on the right side. The attacks were paroxysmal and induced by eating, brushing the teeth, cold winds and touching the lower lip. The pain had not spread. The teeth were extracted in the painful region, but without relief. One year later, an injection of alcohol gave relief for six months. The injections were repeated and gave relief for periods varying from one to three months.

Physical Examination.—The patient was slender and anemic. The lungs and heart were normal. There was mild hypesthesia of the second division on the right.

Operation (Dr. Klemme).—On April 7, 1931, under tribromethanol and local anesthesia, the usual approach to the ganglion was followed. The posterior root

Fig. 25 (case 25).—Another instance illustrating the point in figures 23 and 24.

was exposed, and the inferior outer two-thirds were cut with scissors. Closure was made in the usual manner.

Postoperative Course.—Recovery was uneventful. The area supplied by the third division was anesthetic, and a few fibers from the second division at the corner of the mouth were removed (fig. 25).

CASE 26.—*History.*—A. B., a white woman, aged 64, was admitted to the Barnes Hospital on May 26, 1931, with typical trigeminal neuralgia, primarily of the third division. The family history was irrelevant. The patient's general health had been good. The menopause occurred at 45 years. She had been constipated for years.

The present illness began in 1929, when the patient noticed that an artificial denture, which she had worn for several years without difficulty, began to bother her. After exposure in a rain storm severe shooting pain developed in the left side of the lower jaw. The pain was also precipitated by the taking of food. The

pain recurred every week. She tried home remedies up to December, 1930. She had had treatment of the sinuses without relief. She had constant soreness in the left lip and gum. There was a "trigger zone" below the left corner of the mouth. She had had impaired hearing and tinnitus on the left for many years.

Physical Examination.—The patient was rather slender and of asthenic type; her general physical condition seemed very good. Her heart and lungs were normal. The blood pressure was 202 systolic and 84 diastolic. The peripheral vessels were moderately sclerotic. She had diminished hearing on the left. Stimulation of the lower lip started an attack of pain. Neurologic examination otherwise gave negative results. The patient had major trigeminal neuralgia of the third division, with a spread to the second division. She refused an injection of alcohol and wanted an operation; a differential section was advised.

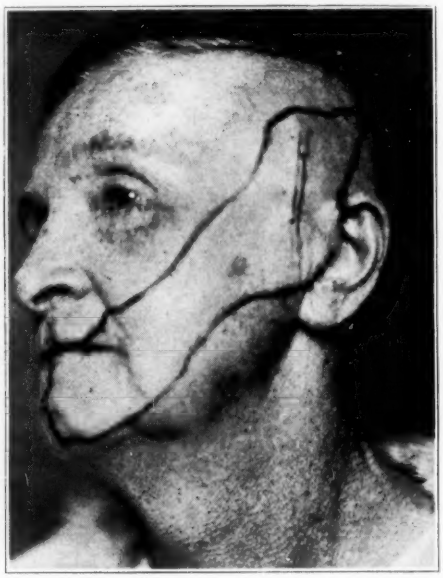

Fig. 26 (case 26).—This too illustrates the point shown in figure 23.

Operation (Dr. Klemme).—On May 28, 1931, under tribromethanol and local anesthesia, the usual approach was made. The middle meningeal artery was sclerotic and tore when an attempt was made to ligate it. The foramen spinosum was plugged with an orris root stick. The posterior root fibers were exposed. Three fourths of the root was carefully isolated and cut with scissors. The motor root was intact. Closure was made as usual.

Postoperative Course.—Recovery was uneventful. Examination disclosed that all the fibers of the third division and only a small portion of those of the second division had been removed (fig. 26). The patient was discharged on the sixth day.

Comment.—This group illustrates the difficulty of being certain that one has isolated and divided all of the fibers of the second division when one is carrying out a subtotal resection of the posterior root. In the desire to leave enough fibers for the protection of the eye, some

fibers of the second division have been left. Separating and leaving only the ophthalmic portion of the posterior root have not been uniformly successful in our hands as perusal of the literature would lead one to believe it should be.

SUMMARY AND CONCLUSIONS

1. There are here recorded the cases of a series of patients on whom a section of the posterior root for trigeminal neuralgia was done, and in whom the sensory loss has been atypical.

2. The portion of the posterior root carrying the ophthalmic fibers is frequently not a separate bundle of fibers.

3. Clinical evidence is brought forward that the arrangement of fibers in the posterior root varies and that fibers interlace or cross, confirming the anatomic work of Frazier and Whitehead.

4. Though some fibers were left in areas in which the patient had pain, the fibers to the area in which the "trigger zone" existed were always cut, and only one of these patients has had a recurrence,[7] thus far, as a result of leaving some fibers. This may mean that some of the pain in cases of trigeminal neuralgia is referred pain. That has been the view expressed frequently in regard to the pain in the first division of which patients complain, and it may also be true of pain in the other divisions.

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7. In case 2 a second operation was performed, but, as stated in the text, there was some doubt in regard to the diagnosis. The patients in cases 1 and 15 were lost track of and did not answer "follow-up" letters, though the former had been followed for a number of years.

TIC DOULOUREUX

ANATOMIC AND CLINICAL BASIS FOR SUBTOTAL SECTION OF SENSORY ROOT OF TRIGEMINAL NERVE

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ANATOMIC CONSIDERATION

By Dr. Spiller

Van Nouhuys [1] has studied the structure of thirty-eight gasserian ganglions. He seems to have done this by observing in ganglions and sensory roots removed from cadavers of adults the course of the nerve fibers as seen by the naked eye or lens in more or less teased preparations. No study of the sensory roots by microscopic sections is reported. In none of the ganglions were there three anatomically separated parts in the sensory root that corresponded to the three terminal divisions of the fifth nerve. The appearance may have been deceptive. One might as readily expect to find the crossed pyramidal tract in the lateral column of the spinal cord anatomically entirely separated from the surrounding fibers, but because it is not one does not deny that this tract has a distinct function. In serial sections of the gasserian ganglion he found no indication that the cell groups represented separate units, or that the interstitial tissue separated definite nerve bundles. I can confirm this observation by my own microscopic examinations of the ganglion. Certain nerve cells of the anterior horns of the spinal cord innervate certain muscle groups, but these groups of nerve cells cannot be separated from other groups under the microscope. The tibialis anticus muscle, from clinical observation, appears to have a distinct group of nerve cells and may be the only muscle paralyzed by acute anterior poliomyelitis, but the nerve cells innervating this muscle cannot be distinguished under the microscope.

From this study van Nouhuys concluded:

1. The sensory root of the fifth nerve is not composed of three parts that correspond to the three peripheral branches from the gasserian ganglion.

Read before the Philadelphia Neurological Society, April 22, 1932.

1. van Nouhuys, F.: The Anatomy of the Gasserian Ganglion: Its Relation to Tic Douloureux, Arch. Surg. **24**:451 (March) 1932.

2. The operation of partial section of the sensory root, assuming that the pain is carried by bundles having a definite location, is not based on anatomic facts, and therefore cannot be regarded as an absolutely reliable procedure.

The method employed by van Nouhuys is that known by German investigators, who have employed it most, as the *Zerfaserungsmethode*. Obersteiner [2] said in regard to it: "It must be well understood that all fiber bundle methods, especially when decussation of nerve bundles occurs, may easily cause deceptive appearance, and for this reason at the present time, possibly unjustly, they have been almost entirely neglected."

Perhaps the most remarkable example in the literature of the error that may arise by a method of this kind is the conclusion reached by von Kölliker [3] in his study of the optic chiasm in man. He employed the methods of Weigert and Golgi in most thorough and exhaustive microscopic technic and came to the conclusion that the decussation of the optic tracts in man is complete and not partial at the chiasm. He says:

Alles in allem kann ich nach den bisher vorliegenden Thatsachen auch für den Menschen unmöglich eine grössere oder nennenswerte Zahl von sich nicht kreuzenden Fasern annehmen. (All in all, it is impossible for me to accept from as yet obtainable facts also for man a considerable or noteworthy number of nondecussating fibers.)

He is speaking of the chiasm, and although he was unable to reconcile his opinion with clinical observation, he held to his anatomic findings.

Obersteiner [4] wrote in regard to this episode: "After the question of semidecussation of the optic nerves in higher vertebrates appeared to have been long decided great interest was aroused when Kölliker again advocated total decussation. The circumstance that semidecussation was questioned by such an authority produced an extensive literature. By all these investigations, in which different methods and different animals were employed, the proof of semidecussation was established, which Kölliker also finally accepted."

In a paper published with Frazier in 1901, I [5] showed, by the method of Marchi, that the location of the degeneration in the spinal root

2. Obersteiner, H.: Anleitung beim Studium des Baues der nervösen Zentralorgane, ed. 5, Leipzig, Franz Deuticke, 1912, p. 6.

3. von Kölliker: Neue Beobachtungen zur Anatomie des Chiasma Opticum, Festschrift zur Feier ihres Fünfzigjährigen Bestehens herausgegeben von der Physikalisch-Medizinischen Gesellschaft zu Würzburg, 1899, p. 111.

4. Obersteiner (footnote 2, p. 502).

5. Spiller, W. G., and Frazier, C. H.: The Division of the Sensory Root of the Trigeminus for the Relief of Tic Douloureux: An Experimental, Pathological and Clinical Study, with a Preliminary Report of One Surgically Successful Case, Univ. Pennsylvania M. Bull. **14**:341 (Dec.) 1901; Philadelphia M. J. **8**:1039, 1901.

depends on the part of the sensory root cut. Bregman obtained similar results. I stated in this paper:

> From the results obtained by Bregman and from mine, we may conclude that the nerve fibres of the sensory root of the fifth nerve, in both its intracerebral and extracerebral portions, maintain the same relative positions throughout the course of this root. This is an important fact, because we may conclude that if the nerve fibres of the sensory root do not mingle freely without regard to order, the nerve fibres of the gasserian ganglion also probably preserve a definite order of arrangement. The nerve fibres passing distally from the ganglion divide into three distinct divisions at the peripheral end of the ganglion. We can hardly suppose that the nerve fibres within the ganglion are arranged without definite order if in both the sensory root and the peripheral divisions a very definite arrangement exists. Tiffany's suggestion to spare the inner third of the ganglion in order to preserve vision seems, therefore, to have an anatomical basis.

In a paper written with Frazier in 1904 [6] I referred again to this experimental work, and stated that, by the method of Marchi, I had found that when only the external part of the sensory root was divided the degeneration in the spinal root of the trigeminal nerve in the pons and medulla oblongata was only in the dorsal part of the root. From this it follows that the fibers of the inner portion of the sensory root occupy the ventral portion of the descending spinal root. Van Gehuchten later carried the experimental work further and determined the position of the degenerated fibers in the spinal root after tearing out the peripheral three divisions of the nerve. I quote from his paper, translated by me in 1904:

> This degeneration of the fibers of the bulbospinal root, after a tearing out of the peripheral nerves, is so constant that we have encouraged one of our students, Dr. Bochenek, to employ this method in determining the situation in the bulbospinal root of the fibers belonging to each of the three branches. The results of his investigations have shown that after a tearing out of the frontal nerve the degeneration is localized exclusively to the ventral portion of the bulbospinal root; after a tearing out of the mental nerve, it occupies the dorsal portion of the same root. The tearing out of the infraorbital nerve is followed by a degeneration of a certain number of fibers in the middle region.

Van Gehuchten confirmed these findings by his own investigations.

Frazier and Whitehead [7] expressed the same opinion regarding the fascicular arrangement throughout the various parts of the trigeminal

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6. Frazier, C. H., and Spiller, W. G.: Physiological Extirpation of the Ganglion of Gasser: Further Report on Division of the Sensory Root for Tic Douloureux, Based on the Observations of Four Cases, J. A. M. A. **43**:943 (Oct. 1) 1904.

7. Frazier and Whitehead: The Morphology of the Ganglion Gasseri, Brain **48**:458, 1926.

nerve and supported their opinion by phylogenetic and embryologic studies. The ganglion was studied from the human fetus to an estimated age of 28 weeks.

In several papers, the first of which appeared in 1908, I [9a] showed that the spinal root of the trigeminal nerve contains pain and temperature fibers and does not contain fibers of tactile sensation.

Ranson [8] stated the belief that the fine fibers that descend directly into the spinal tract of the trigeminal nerve mediate pain and temperature sensations, and that the larger bifurcating fibers mediate tactile sensibility. He referred to my statement that pain and temperature sensibility are mediated exclusively through the spinal tract and nucleus, and that that of touch is mediated through the main sensory nucleus of the trigeminal nerve. This conclusion was indicated in my paper [9a] of 1908; it was elaborated and definitely stated in my paper [9b] of 1910, and again referred to in my paper [9c] of 1915. Winkler reached the same conclusion on this matter five years later in his paper of 1915. In my paper of 1910, I also emphasized that the recognition of contact in the eyeball is through the fibers of pain.

In one of my cases [10] pain sensation in the distribution of the trigeminal nerve was lost when temperature and tactile sensations in the same distribution were intact. This case demonstrated that the fibers of pain sensation must be distinct from those of temperature in the spinal root of the trigeminal nerve, and I showed that it is probable that the fibers of heat sensation are distinct from those of cold sensation.

It is possible that at or near the entrance of the sensory root of the trigeminal nerve into the pons the fibers of touch assume a more internal position, but this by no means implies that a definite arrangement of the fibers for the various forms of sensation does not exist elsewhere in the sensory root. It is probable that the arrangement of the fibers of pain and temperature in the spinal root is similar to that in the sensory root, and is in definite relation to the three peripheral divisions of the nerve. The sensory root on entering the pons behaves in a manner somewhat similar to that of a posterior sensory spinal root on entering the spinal cord.

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8. Ranson, S. W.: Cutaneous Sensory Fibers and Sensory Conduction, Arch. Neurol. & Psychiat. **26**:1122 (Dec.) 1931.

9. Spiller, W. G.: (*a*) The Symptom-Complex of Occlusion of the Posterior Inferior Cerebellar Artery: Two Cases with Necropsy, J. Nerv. & Ment. Dis. **35**:365, 1908; (*b*) Dissociation of Sensation in the Face of the Type Inverse to that in Syringomyelia. The Recognition of Contact in the Eyeball Through the Fibers of Pain, Rev. Neurol. & Psychiat. **8**:68, 1910; (*c*) Remarks on the Central Representation of Sensation, J. Nerv. & Ment. Dis. **42**:404, 1915.

10. Spiller (footnote 9*c*, p. 406).

It is probable that the arrangement of the fibers in the spinal root of the trigeminal nerve in the pons is comparable with that of the spinothalamic tract in the anterolateral column of the spinal cord. I [11] have expressed my views regarding the latter in a discussion on a paper by Wilson and Fay read before the Philadelphia Neurological Society on Jan. 25, 1929, in which I said I believed that the pain and temperature fibers are in contact in the lateral column of the spinal cord but are in separate tracts.

It is well to avoid an error such as that into which von Kölliker fell by ignoring the clinical findings in hemianopia. The clinical results obtained by Frazier in subtotal section of the sensory root are of a scientific value equal to that of those obtained by anatomic or other forms of investigation. If anatomic and clinical findings are contradictory, some mistake has been made in the technic or interpretation of one of the methods.

CLINICAL CONSIDERATION

By Dr. Frazier

From 1901 to 1915 the radical operation universally practiced involved section of the entire sensory root. At that time corneal keratitis was an occasional complication of the operation, and it was with the purpose of wholly preventing this complication that in 1915 I began to conserve the ophthalmic portion of the root (subtotal section) in selected cases.

In 1925,[12] I published my experience with the first twenty-five cases of subtotal section. Ten years had elapsed since the first operation on this series had been performed, and the results in the entire series proved my original supposition; namely, that if the ophthalmic portion of the root is conserved, keratitis as a complication can be eliminated.

In introducing this modification of the then conventional procedure, subtotal section, I was of the belief that the sensory root and ganglion could be dealt with as three separate units. In adopting this hypothesis I was influenced by phylogenetic, embryologic and clinical considerations.

Van Nouhuys takes exception to this hypothesis on anatomic grounds. In opposition to his deductions and the methods by which they were formulated, Dr. Spiller has presented an array of facts and many original observations. In further confirmation of my hypothesis, I here-

11. Spiller, W. G., in discussion of Wilson, G., and Fay, T.: Two Cases of Chordotomy, Arch. Neurol. & Psychiat. **22**:641 (Sept.) 1929.

12. Frazier, C. H.: Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **13**:378 (March) 1925.

with submit clinical evidence. This evidence is derived from a series of cases selected at random from my experience during the past seventeen years.

At first, subtotal section implied section of the outer two thirds of the root. Without attempting to divide the root exactly into thirds, I found that if one or two of the inner fasciculi of the root were left intact there was no loss of sensation in the ophthalmic division and no trophic disturbance of the cornea. I was convinced by my early experience with subtotal section that, at least at the point where the sensory root enters the ganglion, the inner third, the middle and the outer third supplied corresponding portions of the ganglion and the ophthalmic, maxillary and mandibular divisions peripheral to the ganglion. Because of this conviction the principle of subtotal section was given a more exacting test. When the pain was referred only to the third division, only the outer third of the root was divided, and when the pain was referred only to

In *A*, case 17582, the middle third of the root was divided on Sept. 30, 1930; the area of anesthesia was charted on Oct. 29, 1930. In *B*, case 17674, the outer third of the root was divided on Dec. 28, 1929; the area of anesthesia was charted on Jan. 2, 1930. In *C*, case 21122, the inner and middle thirds of the root were divided and the outer third was left intact on Feb. 16, 1931; tested for pain anesthesia eight days after operation.

the second division only the middle portion of the root was divided. With regard to the second division, while an exact subdivision of the root into thirds was not always possible, I found it necessary to leave only one or two fasciculi of the inner and outer portions of the root intact to supply the remaining two thirds of the ganglion. The illustration tells the story. One sees at once that sensation is lost in that peripheral distribution of the trigeminus corresponding to the one third or two thirds of the root sectioned. Whatever may be the deductions from a dissection of the root as practiced by van Nouhuys, the clinical evidence as illustrated by the sensory charts admits of but one interpretation. The outer portion of the root supplies the outer portion of the ganglion and the mandibular division; the middle portion of the root supplies the middle portion of the ganglion and the maxillary division; the inner portion of the root supplies the inner portion of the ganglion and the ophthalmic division.

EFFECT OF ROENTGEN RAYS ON THE CENTRAL NERVOUS SYSTEM

RESULTS OF LARGE DOSES ON THE BRAINS OF ADULT DOGS

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Intracranial roentgen therapy rests on the differential action of roentgen rays on the various structures, normal and pathologic, inside the skull. Information about the effect of irradiation on the normal nervous system has been gathered from experiments with animals and from clinical observations during the treatment of pathologic conditions in man. This paper deals only with the former, reporting the results obtained from heavy dosage with roentgen rays on the brains of adult dogs. The exposures to the roentgen rays were given in the State Institute of Roentgenology, Radiology and Cancer Research in Leningrad, under the direction of Prof. M. I. Nemenov. Physiologic studies of cortical function before and after irradiation were carried out with the use of conditioned reflexes in the physiologic laboratory of Prof. I. P. Pavlov. Histologic examinations of the brains were made in the neuropathologic laboratory of Prof. W. Spielmeyer in Munich.

THE LITERATURE ON ROENTGEN IRRADIATION OF THE CENTRAL NERVOUS SYSTEM OF ANIMALS

Pronounced changes in the development of young animals after exposure of their heads to roentgen rays have been reported repeatedly. There has been considerable discrepancy in the details of the subsequent pathology. Some investigators have described definite alterations in the parenchyma of the brain. Others have failed to find any change in ganglion cells, myelinated fibers or resting glia, but have found lesions in the vascular system or in "labile elements" of the central nervous system, such as the granular cells of the cerebellum.

From the State Institute of Roentgenology, Radiology and Cancer Research, in Leningrad, U. S. S. R., the Physiological Laboratory of the Institute of Experimental Medicine, in Leningrad, U. S. S. R., and the Deutsche Forschungsanstalt für Psychiatrie, in Munich, Germany. The histopathologic study was made by W. Scholz with the aid of the Rockefeller Foundation.

In adult animals, after exposure of the head to irradiation, the experience has been uniform that little or no direct effect of roentgen rays can be demonstrated on nerve cells or fibers, but that it is possible to produce some change in the blood vessels of the brain, together with more or less mesenchymal reaction.

In Russia, in 1896, Tarkhanov [1] observed quieter behavior in flies and delayed reflexes in frogs by the method of Türck after exposure to roentgen rays for from one quarter to one hour.

Rodet and Bertin-Sans [2] began work in France at about the same time. They described paralysis and convulsive movements in small animals after roentgen irradiation, and at autopsy found congestion in the meninges and central nervous system, with hemorrhages and proliferation of cells indicating inflammation. In some guinea-pigs there was meningomyelitis, which was considered not to be an infection in view of sterile cultures in the blood and peritoneal and spinal fluids.

Oudin, Barthélemy and Darier [3] represented the fundamental action of roentgen rays as trophoneurotic in guinea-pigs that presented tremors, changes in tactile sensibility and paraplegias, together with or before the development of skin lesions. Postmortem examinations did not include any detail of the central nervous system.

Jutassy [4] produced paresis in the legs of a rabbit by exposing it to the roentgen rays for ten hours. Histologic examination was made of the skin only, wherein the nerves were reported as normal.

Kienböck [5] found no neurologic signs in guinea-pigs and turtle-doves but did observe quiet behavior, then spastic paralysis and twitching, and finally somnolence and death in white mice after irradiation. An inflammatory change in the central nervous system, or the production of toxins, was postulated.

Rudis-Jicinsky [6] irradiated guinea-pigs and rabbits. After fifty daily exposures, lasting up to ten minutes each, in which the whole animal was exposed, two guinea-pigs died. He reported degeneration in the pos-

1. Tarkhanov, I.: On the Physiological Action of Roentgen Rays on the Central Nervous System, Bolnitsch. gaz. Botkina **7**:753 and 785, 1896.

2. Rodet and Bertin-Sans: Troubles médullaires produit par les rayons de Roentgen, Semaine méd. **18**:195, 1898; cited by Beaujard and Lhermitte: Compt. rend. d. quatrième Cong. franç. de méd. interne, 1898.

3. Oudin, Barthélemy and Darier: Ueber Veränderungen an der Haut und den Eingeweiden nach Durchleuchtung mit X-Strahlen, Monatsh. f. prakt. Dermat. **25**:417, 1897.

4. Jutassy, J.: Die Behandlung der Hypertrichosis mit Roentgenstrahlen, Fortschr. a. d. Geb. d. Röntgenstrahlen **2**:194, 1899.

5. Kienböck, R.: Zur Pathologie der Hautveränderungen durch Roentgenbestrahlung bei Mensch und Tier, Wien. med. Presse **42**:932 and 987, 1901.

6. Rudis-Jicinsky, J.: Experimental Investigations with Roentgen Rays upon Living Tissue, New York M. J. **76**:850, 1902.

terior tracts and in the posterior horns; the central canal seemed dilated with hemorrhages; both animals had extensive burns along the spine.

Scholtz [7] chose four young mice and four young rabbits with fontanels widely open. The heads were irradiated one or more times for one-half hour each at 20 cm. skin distance. In spite of the fact that in one rabbit immediate total paralysis of the hindlegs developed, death occurring the following night, and that two mice and another rabbit died some two or three days later, the author concluded that roentgen rays can exert little or no influence on internal organs, such as the abdominal contents, brain and retina. He went so far as to say that the reports of others to the contrary may be attributed "more to the psychic factor than to any action by the roentgen rays on the organs themselves."

Heineke [8] irradiated white mice and guinea-pigs, using "medium soft and hard tubes." Most of the animals died, the younger dying the earlier. They passed through stages of emaciation, anorexia, apathy and coma, but had no paralyses or convulsions. Adult rabbits were irradiated for forty hours and only severe dermatitis with pyemia resulted. Autopsies on guinea-pigs showed changes in the spleen and lymph glands. Chromophilic changes in cerebral ganglion cells were seen in one case only.

Seldin [9] described changes in mice, but could not find them in guinea-pigs, after repeated roentgen irradiation of the whole body with soft rays. The mice grew emaciated, cowered together and had frowsy hair, and paresis of the hindlegs developed. Autopsy showed congestion in the meninges but no hemorrhages on inspection of the brain. The author concluded that cerebral disturbance was important in the cause of death in these animals.

Försterling [10] reported alteration in the development of young rabbits and puppies after roentgen irradiation. Circus movements developed in one rabbit. The left half of its head had been exposed, and the animal died with the right hindleg in spastic extension. Death with spastic hindlegs occurred in another rabbit, but no histologic study was referred to in the postmortem reports. In view of his results, Försterling advised extreme care in exposing children to roentgen rays.

7. Scholtz, W.: Ueber den Einfluss der Roentgenstrahlen auf die Haut in gesunden und kranken Zuständer, Arch. f. Dermat. u. Syph. **59**:87, 241 and 421, 1902.

8. Heineke, H.: Ueber die Einwirkung der Roentgenstrahlen auf Tiere, München. med. Wchnschr. **50**:2090, 1903; **51**:785, 1904.

9. Seldin, M.: Ueber die Wirkung der Roentgen- und Radiumstrahlen auf innere Organe und den Gesamtorganismus der Tiere, Inaug. Diss., Königsberg, 1904.

10. Försterling, K.: Ueber allgemeine und partielle Wachsthumsstörungen nach kurz dauernden Roentgenbestrahlungen von Säugethieren, Arch. f. klin. Chir. **81**:505, 1906.

Krause and Ziegler [11] made thorough postmortem investigations of other organs in mice, guinea-pigs, rats, rabbits and three dogs, but the central nervous system was only studied incidentally and was not always examined. When mentioned, it was said always to be normal after exposures of different duration to roentgen rays, with the exception of tigrolysis of the anterior horn cells in the cervical cord of one mouse, which was thought to be an artefact.

Sicard and Bauer [12] exposed 2 sq. cm. of the brain or 2 cm. of the spinal cord of dogs. The wounds were then closed merely with muscles and skin. With the rest of the body screened, the sites of previous operation were subjected to repeated roentgen irradiation. Necrosis of the skin with subsequent infection occurred, but they "never observed nervous symptoms which could be attributed to lesions in the cord or brain."

Beaujard and Lhermitte [13] subjected one rabbit to irradiation, exposing the whole animal to 25 Holzknecht units. It died four hours afterward and showed some vacuolar change in the protoplasm of anterior horn cells. A second rabbit received a total dosage of 8 Holzknecht units in seven weeks; on the fifty-third day from the beginning of the treatment it was killed. The protoplasm of the cells in the anterior horns had a dusty appearance. Some cells were shrunken, some normal. The central canal was dilated and filled with fine albuminoid granules. There was diffuse degeneration in the posterior and lateral columns (Marchi stain).

Labeau [14] is often referred to as having described macroscopic and microscopic damage to the spinal cords of young animals, but not to those of adults. The original article was not available to us.

Turner and George [15] exposed a litter of rabbits, 6 weeks old, to the roentgen rays. A complete study was made on only one rabbit. It received three exposures at intervals of one week, each of about a Sabouraud dose, on the right side of the head. The left iris turned gray; epilation took place on the right side of the head, and then later the right iris also changed color. It was killed on the fifty-fourth day. The brain was

11. Krause, P., and Ziegler, K.: Experimentelle Untersuchungen ueber die Einwirkung der Roentgenstrahlen auf tierisches Gewebe, Fortschr. a. d. Geb. d. Röntgenstrahlen **10**:126, 1906-1907.

12. Sicard and Bauer: Effets des rayons sur la moelle et le cerveau chez le chien, Rev. neurol. **15**:903, 1907.

13. Beaujard, E., and Lhermitte, J.: La radiothérapie de la syringomyélie, Semaine méd. **27**:193, 1907.

14. Labeau, cited by Wetterer, J.: Handbuch der Roentgen- und Radiumtherapie, Leipzig, Keim und Nemnich, 1922, vol. 1, p. 424.

15. Turner, D. F. D., and George, T. J.: Some Experiments on the Effects of X-Rays in Therapeutic Doses on the Growing Brains of Rabbits, Brit. M. J. **2**:524, 1910.

smaller on the exposed side, and the pyramidal cells were less well "developed," less numerous and more vacuolated and took stains less well. Also the blood vessels were slightly "smaller" on the exposed side.

Beier [16] made circular holes, from 10 to 12 mm. in diameter, in the midline of the skulls of rabbits. He then irradiated with 1¼ to 2¼ erythema doses through those openings, the rest of the animal being shielded. None of the rabbits developed paralysis or convulsions. From seven to twenty-three days after irradiation they were killed. Autopsy showed in the first rabbit an area of necrosis surrounded by a zone of reactive inflammation in the brain at the site of the trephine. This was considered to be due to trauma rather than to the direct action of the roentgen rays, since it occurred in this animal only. The other rabbits showed inflammatory infiltration of the pia but no definitely abnormal changes in the brains. Ganglion cells (Nissl), myelin sheaths (Weigert), neurofibrils (Bielschowsky), lipoids (Marchi) and the blood vessels were reported to be normal. The only questionable features consisted of somewhat more neurophagocytosis and more binuclear ganglion cells in the irradiated than in the nonirradiated brains.

Walter [17] reviewed the work that had been done by others and included the results of roentgen irradiation of dogs by Krukenberg with the pathologic examinations made on them by Müller-Elberfeld. The fore part of one puppy was exposed and the hind part of the other. When the former grew it resembled a rabbit, and the latter a hyena. Only in the former did ataxia, tremor, loss of vision and salivation develop; the dog walked in ellipses and frequently fell over. There was pallor of the optic disks. At autopsy, little cerebrospinal fluid was found, the skull cap was thin, the optic nerves were definitely smaller than normal, and the brain weighed less than that of the other dog. Walter found no histologic changes in the central nervous system. He then made experiments on rabbits, dogs, guinea-pigs and lambs, but did not add anything new on the effect of roentgen rays on the nervous system.

Following repeated irradiation with an effective dose of from 1 to 16 units (Bordier) on the spinal cords of dogs and guinea-pigs, Balli [18] observed pareses of the extremities, emaciation and anemia. The rete fibrillare in some of the most intensely irradiated cells was shown by the method of Donaggio to have thickened filaments and a narrow mesh,

16. Beier, J.: Ueber die Wirkungen der Roentgen- (und Radium) strahlen auf das Zentralnervensystem, insbesondere das Gehirn, Inaug. Diss., University of Zurich, Wiesbaden, R. Bechtold & Company, 1910.

17. Walter, R.: Ueber Wachstumsschädigungen junger Tiere durch Roentgenstrahlen, Fortschr. a. d. Geb. d. Roentgenstrahlen **19**:123, 1912.

18. Balli, R.: Roentgenstrahlen und Rete neurofibrillare endocellulare bei erwachsenen Säugetieren, Strahlentherapie **6**:443, 1915.

giving a somewhat granular appearance, particularly around the nucleus. In other parts of these cells, the elective stain was taken poorly. In some places there were clear or light blue zones of different sizes which looked like vacuoles.

Brunner [19] reviewed the literature and reported his own experiments on kittens and puppies. The heads of two kittens, 11 days old, were given a single exposure of 4 erythema doses (40 Holzknecht units), with a 3 mm. aluminum filter. Both animals became emaciated; tremors and conjunctivitis developed, and one of them grew blind. Autopsy showed an increase of glia cells in the spinal cord, focal thickening of the meninges, isolated areas of edema and fresh hemorrhages. In the cerebellum of each kitten the granular layer was thin and in places absent. Four puppies of a 4 day litter were then irradiated with fractional doses. The first received four exposures of 7, 7, 9 and 4 Holzknecht units, respectively; it died in status epilepticus fifteen days after the first irradiation. At autopsy there were congestion and hemorrhages in the meninges, gray matter of the cord and cerebral cortex. The second puppy was also irradiated four times. Epileptic attacks then developed two weeks after the first exposure and when the animal was killed, a few days later, a massive edema and anemia of the brain with extensive hemorrhage into the fourth ventricle were found. There were congestion and hemorrhages in the meninges, spinal cord, brain stem, cerebellum, cerebral cortex and choroid plexus. The superficial granular layer in the cerebellum was completely absent. The cortex was small and showed an increase of perivascular glia. The third puppy was irradiated three times. Two weeks after the first irradiation it became somnolent, but whined as though in pain. Then tremors, clonic twitchings and dysmetria developed, and it walked in circles. Seven weeks after irradiation, loss of sight was noted, while hearing was retained. The dog was killed on that day and showed at autopsy congestion and occasional hemorrhages in the meninges and cortex, and a local increase of perivascular glia, but the ganglion and glia cells were normal. The fourth puppy was irradiated only once. Sleepiness, tremors and apparent decrease in olfactory acuity and difficulty in regulating its body temperature developed, so that the dog was kept in a warm room. It was not killed. Later growth seemed to be quite normal, but the dog is said to have been sterile. After a discussion of the action of the roentgen rays, Brunner drew the conclusions that, in the parenchyma of the brain, only elements that show a certain lability are affected, particularly the superficial granular cells in the cerebellum. Fixed structures such as ganglion cells, myelinated fibers and resting glia show no change. In the new-

19. Brunner, H.: Ueber den Einfluss der Roentgenstrahlen auf das Gehirn, Arch. f. klin. Chir. **114**:332, 1920.

born, irradiation causes no pathologic change in the blood vessels but much active hyperemia, which may in turn produce a high grade of edema and even hydrocephalus internus. Secondary to the intense congestion—or perhaps due to the presence in the blood of choline liberated during radiation—hemorrhages and a relatively high percentage of polymorphonuclear cells are found in the swollen capillaries. In regard to Brunner's work, attention is called particularly to the very young age of his experimental animals, the high roentgen dosage which they received, and the fact that he killed them with chloroform prior to making his histologic studies.

In another paper, Brunner [20] reported the introduction of sterile celloidin prisms into the brains of rabbits and dogs. He then exposed the site of operation in some of these animals to the roentgen rays. All the animals were then killed and comparison of the irradiated with the nonirradiated brains showed that, in the former, polymorphonuclear cells played a more active rôle in reparation, which was postulated as due to a possible increase in circulating lecithin. However, there was no difference in the regenerating glia or connective tissue in the two sets of brains.

Demel [21] studied three litters of puppies, the first two when 4 days old, the third litter when 2 weeks old. He subjected them to four roentgen exposures at intervals of four days, giving ⅔ skin unit dose at each sitting, with a 3 mm. aluminum filter, at 25 erythema doses. The whole head was irradiated in the case of the first two litters (six pups), while only portions of the heads were left unscreened with the third litter (seven pups). Eight weeks after irradiation, the exposed puppies were smaller than the controls; the subcutaneous tissues retained good proportions, but the bones were shorter and more delicate, and the weight of the irradiated group was less than that of the nonirradiated. An ataxic gait might develop. The puppies walked on a wide base, veered to one side and often fell over, and when they ran the legs crossed. No epileptic attacks were observed. At autopsy, the cerebrum and cerebellum of the irradiated animals were smaller than in the controls, and showed "pachygyria." In serial sections of the brains of the first litter, killed five months after irradiation, there was reduction in the size of the pyramidal cortex, cerebral peduncles and corpus geniculatum mediale and of the region of the corpora quadrigemina and the corpus restiforme. The right side of the head had received more intense

20. Brunner, H.: Der Einfluss der Roentgenstrahlen auf die Regenerationsvorgänge im Gehirne mit besonderer Berücksichtigung der Neuroglia, Arch. f. klin. Chir. **116**:489, 1921.

21. Demel, R.: Tierversuche mit der Roentgenbestrahlung des Cerebrum, Strahlentherapie **22**:333, 1926; Die Wirkung der Roentgenstrahlen auf das wachsende Gehirn im Tierversuch, Zentralbl. f. Chir. **56**:1176, 1929.

irradiation, and in each case the right hemisphere was smaller than the left. The basal ganglia appeared normal. In single sections from the brains of the other pups, killed from nine to seventy days after irradiation, there was diffuse disappearance of cells in all layers, which was more marked near the surface. In these places the molecular zone was relatively wide. Areas were also found in which there was marked destruction of the cortical architecture, appearing both as indistinct stratification of the layers and as diffuse alterations in the cells. These cells showed "degenerative" changes with vacuolization. There were no inflammatory processes and no special changes in the blood vessels or glia. When the whole heads had been irradiated, changes developed in the eyegrounds comparable to "optic neuritis" in man. The only parts of the brains that had an abnormal contour were the occipital lobes, where the convolutions were fewer than normal, and sulci were barely indicated. Since the hippocampal region was always fully developed, Demel suggested that the roentgen action may affect the phylogenetically newer structures to a relatively great extent.

On irradiation of the kidney region of various animals, Gabriel [22] noted paralytic symptoms in the hindlegs of one dog, five months after a single exposure to 4½ erythema doses. Then a bladder infection appeared. He found hyperemia, especially in the anterior horns of the lumbar cord corresponding to the zone of epilation. The blood vessels in the meninges were dilated, and there were hemorrhages into the spinal cord. The ganglion cells showed no abnormality. He regarded the changes in the kidney, liver, adrenals and spinal cord as further evidence in favor of the conclusion that the roentgen action is primarily on the vegetative nerves that control the tone of the vascular walls—a proposition previously developed in conjunction with David.

Mogilnitzky and Podljaschuk [23] exposed sixteen dogs and twenty-four rabbits to roentgen rays, at a tension varying between 120 and 180 kilovolts, and with filters that were either 3 mm. aluminum or 1 mm. aluminum plus 0.5 mm. zinc. Animals that lived longer than one month showed more or less inhibition of normal growth and relative loss of weight, but as some adiposity was also observed, the reduction in weight was attributed merely to their small size, presumably due to damage to the posterior lobe of the hypophysis. Apathy and weakness were noted, but no epileptic attacks were seen. In a few animals, however, there was some "hyperkinesis" in the legs. A group of adult dogs received irradiation through three portals, each of 1 to 1½ erythema doses. These dogs were observed for from sixty to eighty-five days. At

22. Gabriel, G.: Die Beeinflussung von Tierorganen durch Roentgenbestrahlung, Strahlentherapie **22**:107, 1926.

23. Mogilnitzky, B. N., and Podljaschuk, L. D.: Zur Frage ueber die Wirkung der Roentgenstrahlen auf das zentrale Nervensystem, Fortschr. a. d. Geb. d. Roentgenstrahlen **40**:1096, 1929.

autopsy, the meninges were thickened at the sites of irradiation; there were thickening of the adventitia of the medium-sized and larger blood vessels, an increase in the number of cells in the vessel walls, some perivascular increase in glial elements and a mesenchymal-glial muffing around the vessels; droplets of fat were seen here and there in the capillary endothelium. These mesenchymal changes varied in extent and location, and the variations were regarded as the explanation of discrepancies in previous reports. In no adult animal of this group were ganglion cells, neurofibrils, mitochondria or cells of the choroid plexus affected. Another group of adult dogs received irradiation through two portals, each from 2 to 3 erythema doses. Observation lasted for eighty-five days. Autopsy showed slight infiltration and thickening of meninges, focal swelling and deposits of fat droplets in the endothelium of capillaries and smaller vessels, occasional proliferation of endothelium and perivascular glial proliferation. These changes were particularly evident in the thalamus. Again no abnormality in ganglion cells or in cells in the choroid plexus was seen. In another series of dogs, single exposures of the medulla at 5 erythema doses resulted in a little widening of perivascular spaces and slight perivascular glial proliferation. Single exposures of the spinal cord to 5 erythema doses were followed by dilatations of the central canal, with proliferation of ependymal cells, glia and capillaries in its region. A group of puppies presented different results from those found in adult dogs. The pups were 5 weeks old, received irradiation through three portals at 1 erythema dose each, and were observed up to one hundred and thirty-four days after exposure. In the brains the mesenchymal reaction was comparable to that of the adult dogs, but in addition there were distinct changes in the parenchyma of the brain, such as disturbance of cyto-architecture, focal deficits of cells in the superficial layers and "degenerative-atrophic" changes in the ganglion cells. Finally, a group of rabbits was given irradiation in single large doses, from 3½ to 10½ skin unit doses. Most of these animals died spontaneously a few days after exposure. The brains showed vascular changes, varying from hyperemia with slight swelling of the capillary endothelium to large hemorrhagic areas, although the continuity of the vessel walls in these areas always seemed intact, suggesting that the roentgen effect was a physicochemical one, which increased the permeability of the capillaries and thus allowed the hemorrhagic exudation. The final conclusion is that one can penetrate the "hemato-encephalic barrier" with roentgen rays without doing damage to the parenchyma of the adult brain.

Rachmanow [24] injected trypan blue subcutaneously into white mice. On exposing the body but not the head to roentgen rays, the dye did

24. Rachmanow, A.: Zur Frage ueber die Wirkung der Roentgenstrahlen auf das Zentralnervensystem, Strahlentherapie **23**:318, 1926.

not appear to be increased in the brain and meninges. But, on exposing the head and shielding the body, more vitally stained endothelial cells and histiocytes were found in the pia in irradiated than in non-irradiated mice. In the brains of these animals, blue clumps appeared in histiocytes, especially in the white substance and in the region of the tuber cinereum, and scattered through the brain there were small light blue deposits of different size in the walls of the blood vessels. The distribution was not uniform, and no reason was found for the inequality.

In 1930, Mogilnitzky and Podljaschuk [25] reported the injection of trypan blue or a solution of ferrum oxydatum saccharatum into rabbits and dogs. Single or repeated roentgen exposures of the heads were also made at different times in relation to the injections. Although single irradiations were ineffective, repeated doses of roentgen rays altered the usual reaction of the mesenchymal elements in the brains, so that trypan blue or iron could be demonstrated in the vascular endothelium and in perivascular glia cells. These reactions came out best when from three to five roentgen exposures were made daily or every other day, the dye being injected on the day after one roentgen irradiation and the day before another. Three days after the injection, the tissues showed the color, which soon disappeared, to reappear again some twenty to thirty days later if a further series of irradiations was carried out. This work is offered as additional evidence of the action of roentgen rays in breaking down the hemato-encephalic barrier.

In the *Jahrbuch für Roentgenologie,* 1931, reference is made to work by Perotti,[26] in which microglia is said to be sensitive to roentgen irradiation. The original article is not at our disposal.

An interesting clinical observation by Marburg [27] led to experimental studies on the effect of roentgen rays in temporarily suppressing the production of cerebrospinal fluid and in relieving patients with headache due to increased intracranial pressure. Inaba, Sgalitzer and Spiegel [28] inserted a cannula through the atlanto-occipital ligament of dogs, draining fluid drop by drop from the cisterna cerebellomedullaris. After establishing normal curves, they exposed the whole heads of the dogs to 80 per cent of an erythema dose. The curves then became lower in parts or throughout, especially when irradiation occurred from

25. Mogilnitzky, B. N., and Podljaschuk, L. D.: Roentgenstrahlen und sogenannte "hämato-enzephalische Barriere," Fortschr. a. d. Geb. d. Roentgenstrahlen **41**:66, 1930.

26. Perotti, cited in Jahrb. f. Roentgenol. **2**:16, 1931.

27. Marburg, O.: Versuche einer nichtoperativen Beeinflussung hirndrucksteigender Prozesse, Wien. klin. Wchnschr. **37**:1017, 1924.

28. Inaba, C.; Sgalitzer, M., and Spiegel, E. A.: Ueber den Einfluss von Roentgenstrahlen auf die Liquorproduktion, Klin. Wchnschr. **6**:1655, 1927.

ten to fourteen days before the fluid was measured. Since the choroid plexus is believed to form the cerebrospinal fluid, microscopic examination of its cells was made. Their nuceli appeared slightly pyknotic, and slight changes were noted in the cellular protoplasm. As a result, roentgen rays were considered to diminish the production of cerebrospinal fluid by direct action on the cells of the choroid plexus.

Heidrich, Haas and Silberberg [29] were unable to confirm this theory. They made intrathecal punctures at frequent intervals in twelve dogs with previous lumbar laminectomy and could find no alteration in the amount of fluid which flowed after exposure to 9 erythema doses through three portals of entry to the head. All the animals were followed for three months and some for a year. The conclusion states that neither the clinical experience nor the experimental and histopathologic studies (including vital staining with carmine) provide any proof that a significant effect is obtained with roentgen irradiation of the choroid plexus. But the authors add that further experience is necessary.

König and Panning [30] found vacuoles in the cells of the choroid plexus of rabbits the heads of which had not been exposed to roentgen rays, and these investigators could not discover any change in the appearance of the choroid plexus in irradiated rabbits.

No attempt is made to review the literature on the action of roentgen rays on the eye or vegetative nervous system or to refer to the papers that deal with the effect of radium on the nervous system.

EXPERIMENTAL PROCEDURE

The general plan of work reported in this paper called for an initial period during which a series of stimuli was given almost daily to dogs and the resulting conditioned reflexes were recorded. The technic was the usual one employed in the laboratory of Professor Pavlov.[31] Since these dogs had all been used before in other studies with conditioned reflexes, the preliminary period in each case lasted just long enough to accustom each dog to the new order and arrangement of stimuli chosen for the experiments. These first observations provided a standard of comparison for the conditioned reflexes obtained after irradiation. Details in each case appear in the description of results and on the charts. In general, a routine schedule was adopted for each dog, and the same stimuli were then applied in the same order and timing, and at about the same time of day. Only in the case of one dog, studied for six months after irradiation, was the usual schedule broken from time to time, always to return to the original plan of work.

The aim was to stress visual, but also to have auditory and tactile, stimuli represented in the interest of localization. Moreover, each day's experiment began

29. Heidrich, L.; Haas, M., and Silberberg, M.: Zur Frage der Plexusbestrahlung bei chronischem Hirndruck, Beitr. z. klin. Chir. **145**:285, 1928.

30. König, E., and Panning, G.: Zur Roentgenbestrahlung der Plexus chorioidei, Deutsche Ztschr. f. Chir. **218**:375, 1929.

31. Pavlov, I. P.: Conditioned Reflexes, translated into English and edited by G. V. Anrep, London, Oxford University Press, 1928.

and ended with a "strong" stimulus, such as the sound of a bell or metronome, which experience has shown can be counted on to produce a relatively large conditioned salivary response. The other stimuli were "strong" and "weak." The latter included light, a "pure" tone produced by an oscillator and microphone and tactile stimulation. None of these normally gave consistently large conditioned reflexes. The sight of rotating feathers is an exception among visual stimuli, for it alone is "strong." In the apparatus used in this work it was accompanied by a very faint sound from the clockwork that drove it, but the sound of the mechanism alone without rotation of the feathers failed to produce any conditioned responses in two of the dogs with which this stimulus was used. Finally, with all dogs some one stimulus was repeated once in each experiment, merely for the comparison in size of a first and second trial.

The dogs were exposed to roentgen rays under anesthesia. When anesthetized, each dog was placed in a box, and a plaster cast was put around the muzzle and neck so that the whole head was immobilized. Localizators then directed the roentgen rays with a cross-fire through five portals of entry, the center of which was aimed at the occipital lobes in each case.[32] The posterior part of the head doubtless received considerable irradiation throughout, but the occipital lobes and the cerebellum certainly received the heaviest dosage.

Daily observations were made on the conditioned reflexes, the results of which appear on the charts. These charts present each stimulus separately in the order given in the daily experiments. The range of the normal conditioned response to each stimulus, as determined before irradiation, appears as a band of coordinate ruling carried horizontally across the chart. The lower line at the bottom of each ruled strip represents the normal minimal conditioned reflex and that at the top gives the normal maximum. The normal numerical average of the conditioned reflexes to each stimulus prior to irradiation is given as a horizontal line, labeled as such. The unconditioned salivary reflex, in terms of the amount of saliva secreted during the first minute after food was given to the dog, is represented at the bottom of each chart. On this background of normal values, the reading of every single conditioned reflex obtained after exposure to the roentgen rays has been plotted to scale. The unconditioned secretion appears as the numerical average of the successive unconditioned readings made during the day's experiment, and it is plotted to a smaller scale than are the conditioned reflexes. Each vertical division on the coordinate paper represents a day, and the lapse of a seven day week is indicated by darker and longer vertical ruled lines.

The dogs were killed at different periods after irradiation by cutting the throat and great vessels of the neck, without an anesthetic. The whole brains of dogs 1 and 2 were put directly into formaldehyde. The brains of dogs 3 and 4 were divided in the midline. Sections were taken at once from the frontal, central, postcentral with temporal, and occipital lobes and from the cerebellum, and these were put into 96 per cent alcohol. The rest of these brains went into formaldehyde. The salivary glands and sections from the internal organs were put into Zenker's or Müller's fluid for histologic study.

RESULTS OF THE ROENTGEN IRRADIATION

Dog 1.—Although active and strong, this animal would often crouch when approached. He was slow to develop his first conditioned reflexes, seven months before exposure to the roentgen rays. At the start, the unconditioned salivation was scanty; then it slowly increased as time went on until it was about three times

32. E. I. Mikhaelova conducted the technical part of the irradiation.

the amount originally secreted during the first minute after food was given. Moreover, the dog refused food when some new stimuli were given for the first time. On one occasion, two and a half months before irradiation, when a series of stimuli was not reinforced as usual with food ("extinction test"), the conditioned reflexes became absent or negligible for the following four days. However, at this time the saliva became purulent, so a temporary inflammation of the gland or duct may account at least in part for the altered salivary reflexes. This was the only time when any established conditioned reflexes were absent for two consecutive days. But there were two other isolated unexplained zero readings with the reflex to tone during the period of preparation for this present work. Thus, previous experience with this animal had repeatedly shown that he was a dog of strongly inhibitive type (Pavlov), and that any new situation might reduce or even abolish the conditioned reflexes for a time. In such a dog, the anesthesia and prolonged immobilization during the irradiation might be expected to decrease the conditioned reflexes merely by exaggerating the tendency toward functional inhibition that goes with his type.

On Jan. 20, 1931, the dog was anesthetized with 10 cc. of a 2 per cent solution of morphine subcutaneously and 210 cc. of a saturated solution of chloralose (a little over 1 Gm.) intravenously, and was then irradiated through five portals for an hour each, the cross-fire centering on the occipital lobes. The diameter of the localizator was 1 cm., distance to the skin 23 cm., tension 152.5 kilowats, current 4 milliamperes, and filters 0.5 mm. zinc and 3 mm. aluminum. That gave at the surface a total of 20 human erythema doses. Immediately after the irradiation, there was considerable edema of the tongue, palate, sublingual glands and soft parts around the muzzle, but on the following day this had completely disappeared.

The results of the conditioned reflexes, before and after irradiation, appear in figure 1. On January 23, the dog appeared tired during the experiment and lay down between stimuli on the stand, but took food when it was offered. It was not until January 25 that he kept his usual standing position and ate with avidity again throughout the experiment. All conditioned reflexes were small or absent immediately after the irradiation. Then the first daily stimulus, a metronome, which is a "strong" stimulus, brought out a reflex that grew larger from day to day until it reached the normal average size. But the same metronome stimulus in the last place on the daily schedule began to be followed by a small reflex on January 24. The three visual stimuli (one to light and two to rotating feathers) remained absent at all times after the irradiation. And yet it was noticed on the last day of the experiments that the dog turned the head a little, looked directly at the rotating feathers when the stimulus was given, and remained looking at them even after food appeared. It seems that the dog saw the feathers rotate although there was no conditioned salivary reflex. The reflex to "pure" tone was always somewhat uncertain in this dog, but it was never minimal or absent for five days in succession before exposure to roentgen rays. The general playfulness and appearance of the animal were normal after January 25. On January 26 and 27, the unconditioned reflex was normal in size, and so it seems likely that the slightly low unconditioned readings earlier in the week merely expressed a low level of general bodily vigor. In this rôle they would represent reduced subcortical excitability rather than damage to the salivary glands themselves as a result of roentgen irradiation.

The dog was killed on January 27, seven days after the exposure to the roentgen rays.

Dog 2.—This animal was always very active and restless. He learned the significance of new conditioned stimuli quickly, presented conditioned reflexes

which could be counted on to be large although not exactly the same size from day to day, produced appreciable amounts of saliva in the intervals between stimuli, and during the experiments moved around a good deal and often scratched at the balloon that collected the saliva on his cheek. This dog was of the excitable type (Pavlov). Apart from a long-standing limp with the left hindleg, the cause of which was unknown, nothing was observed either in the conditioned reflexes or in the behavior which suggested any disability during the eight months prior to irradiation during which he was under observation in the laboratory.

On Jan. 20, 1931, the dog received 10 cc. of a 2 per cent solution of morphine subcutaneously and 200 cc. of a saturated solution of chloralose intravenously and, two hours later, 6 cc. of the 2 per cent solution of morphine subcutaneously. Irradiation was carried out much as with dog 1—five portals of entry, with cross-fire centering on the occipital part of the brain, the diameter of the localizator

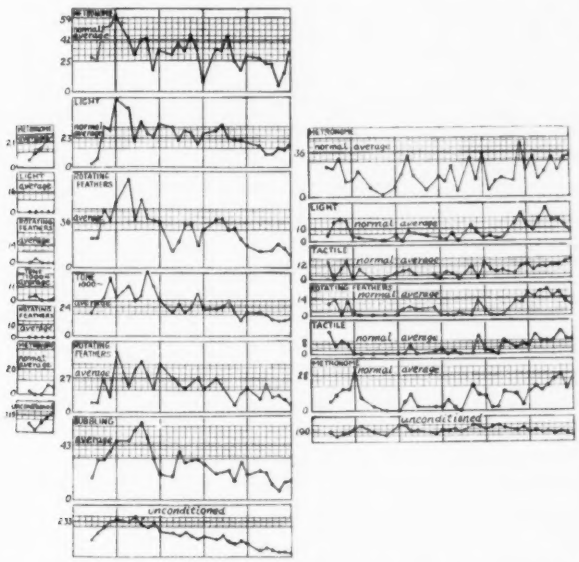

Fig. 1.—Record of the conditioned and unconditioned reflexes, before and after irradiation, in dogs 1, 2 and 3, reading from left to right.

being 1.5 cm., duration one hour through each portal, distance to skin 35 cm., tension 152.5 kilowats, current 4 milliamperes and filters 0.5 mm. zinc plus 3 mm. aluminum. There was a total of 20 human erythema doses at the surface.

The record of the salivary reflexes after exposure to roentgen rays appears in figure 1. On the third day after irradiation, the dog ate promptly and his behavior was quite as usual. Most of the conditioned reflexes on that day were a little below the previous minimum, and the unconditioned reflexes, which serve as an indicator of appetite and of the functional integrity of the salivary gland itself, were slightly low. Then the reflexes began to rise, and on the seventh day after irradiation five of six of the conditioned reflexes were larger than the normal maximum, while the unconditioned salivation remained within the usual limits. For a little over a week, the salivary secretion to conditioned stimuli remained large, while that to food continued near the usual average. During that period there were a few

days with a record of excessive interval secretion. Then on the fourteenth day after irradiation, the unconditioned secretion began to fall and showed a slow but fairly consistent decrease to the time of death. This is presumptive evidence of action by the roentgen rays on the salivary glands, since no change was observed in the dog's general behavior in the chamber during work or in his apparent eagerness to eat when food appeared. On the sixteenth day after irradiation, some few of the conditioned reflexes began to give low readings, which continued intermittently and irregularly. The first sign of epilation appeared on the twentieth day. It increased day by day until the back of the head was bare between the ears and down on to the neck. Red, moist areas developed and went on to superficial sloughing on about the twenty-fifth day, especially at the sites of previous roentgen exposure. They dried up to a large extent after a week or so, leaving crusts which marked the spots on an otherwise smooth surface of epilation. In the meantime the unconditioned salivation was definitely reduced in amount and the conditioned reflexes gave low readings more frequently, though inconstantly. All conditioned reflexes were below the normal minimum on the thirty-second day after irradiation, and most of them remained so until the animal was killed. The conditioned stimuli which produced the greatest change after irradiation were the rotating feathers (regarded as a "strong" visual stimulus), the sound of bubbling (a "strong" auditory stimulus, which is significant in these experiments in being placed last in the daily series) and a "pure" tone (a "weak" stimulus for many dogs, having as a rule a small or inconstant effect on the salivary reflexes). On the other hand, although it is a "weak" visual stimulus and in spite of maximal roentgen exposure to the occipital lobes, the reflex to light never dropped consistently below normal values. The light stimulus, however, was given daily in second place on the schedule. Salivary reflexes in this place are commonly the largest of all. With this dog, the light stimulus in second place was followed by the smallest of all the salivary responses before irradiation, and after irradiation it droped the least of all.

This dog was killed on February 24, five weeks after the exposure to the roentgen rays.

Dog 3.—This was a strong animal, which allowed a few persons to handle him, fiercely attacked others and actually bit several people connected with the laboratory. He developed some conditioned reflexes unusually rapidly (to metronome, bubbling and rotating feathers), while others never became really reliable (tone and light). One individual peculiarity was the fact that rotating feathers, a "strong" stimulus with most dogs, produced conditioned reflexes in this dog quickly when the reflex was first being established, but the size of the salivary response never became large enough to class the stimulus as a really "strong" one for this dog. At the time of the experiments reported here, there was almost no interval secretion. Nine months before irradiation, the unconditioned reflexes were relatively small. They grew slowly until about two months before irradiation when they were nearly three times their original size. Then they dropped at the time of these experiments to about twice the initial amount. Moreover, successive repetition of identical stimuli, or at least of the same daily order of stimuli, proved especially effective in the development of new conditioned reflexes and in the production of relatively large amounts of saliva in the ordinary routine. There were a few occasions when noises in the room outside the work chamber led to partial or complete suppression of conditioned reflexes. Further, one low conditioned reflex showed a tendency to reduce the next, even when the latter was brought out by a "strong" stimulus. While a series of eight successive stimuli with only the metronome gave reflexes of similar size, those with bubbling were smaller than usual and somewhat irregular, and those with tone fairly regular after an initial

zero. A few days later, in a single experiment, the metronome stimulus was given twice with ordinary reinforcement; then a different stimulus; then the metronome again, but this time continued without stop and without reinforcement with food until the conditioned secretion became completely extinguished (zero reading), which occurred in seventy seconds; then a different stimulus; then a final trial with the metronome, which produced an appreciable conditioned reflex. This was the procedure advised by Pavlov in order to determine the physiologic type of the dog. The result indicated that it was a dog of balanced type, but leaning distinctly in the inhibitive direction.

In January, five months before irradiation, there was a period of three weeks during which there was a change in the behavior of this previously self-assertive dog; he dropped his former aggressive behavior, did not want to work, would sit on the floor with his head down instead of running to jump up on the stand as he used to do, wanted to be stroked and petted and appeared fatter. But once the experiments were begun there were prompt and marked motor conditioned reflexes, although the salivary reflexes were small for several days. A gradual return to more active behavior and to the exhibition of fairly reliable conditioned salivary responses then took place. They remained reasonably constant up to the time of irradiation. The significance of this period is not certain. The temporary change was similar to the so-called "neuroses" that have often been commented on in these laboratories, but in view of the postmortem observations we are forced to consider the possibility of a mild encephalitis, from which the dog apparently recovered before preparation for the irradiation.

On June 10, 1931, the dog was given in divided doses about 2 Gm. of sodium amytal, partially intravenously and partially intramuscularly, for anesthesia. He was then exposed to roentgen rays through five portals, forty-four minutes each, centering on the posterior part of the brain. The diameter of the localizator was 2 cm., distance to skin 24.5 cm., tension 180 kilowats, current 5 milliamperes and filters 0.5 mm. copper and 3 mm. aluminum. There was a total of 20 human erythema doses at the surface. Immediately after irradiation there was some edema of the tongue and palate, which disappeared completely overnight.

The record of the conditioned and unconditioned reflexes appears in figure 1. On the second day after irradiation the dog was ready to begin experiments again, but reliable results did not begin until the third day. Then the tendency for the conditioned reflexes to drop began and continued for a week. Different stimuli produced low responses on different days. Ten days after irradiation all the conditioned reflexes were below the normal minimum, three of them giving zero readings. On the twelfth day a row of zeros was recorded, involving all the conditioned reflexes except the first, and even that was less than a whole drop of saliva. The first sign of epilation was also noticed on the twelfth day. It began on the left side of the head where the cement was used to hold the rubber tubing of the balloon to the hair. It gradually spread on the left side and at the single midline field of radiation. Red moist areas developed on the twentieth day, without any slough, and they soon dried up, leaving crusts which marked the portals of entry for a few more days. The parotid duct opened on the left cheek, so that the saliva was collected from the gland on the side of the more pronounced skin reaction. Epilation at the portals of entry began on the right side of the head on the twenty-fourth day and slowly spread until the vertex and most of the back of the head were bare. After the fifteenth day, the first stimulus (metronome) began to take on appreciable values, although still below normal limits until the twenty-sixth day after irradiation, when it reached the normal zone. The rest of the conditioned reflexes fluctuated but remained small. Another low point occurred on the twenty-ninth

day. Then gradually and irregularly the reflexes crept up until about five weeks after irradiation, when they were essentially normal. The conditioned stimulus which was the last to give stable salivary reflexes was the metronome, in the first as well as in the sixth place on the daily list. Throughout the experimentation the unconditioned reflexes remained virtually within the normal limits, and accordingly there is no physiologic reason for suspecting any significant direct influence of roentgen irradiation on the salivary gland itself.

A point of interest is the comparison between the motor and salivary reflexes. For a short period, several months before irradiation, it was noticed that as soon as a stimulus was given this dog would immediately move his head in the direction of its source, and then after about fifteen to twenty-five seconds would bring his nose to the pan and wait for the food to appear. At the same time the salivary conditioned reflexes were minimal. It has already been suggested that the dog may have had a mild encephalitis at that time. At any rate, the same discrepancy between pronounced motor and minimal or absent salivary conditioned reflexes was also noticed in these experiments. From the twelfth day after roentgen irradiation, the dog was observed with this particularly in view, and the motor reflexes were repeatedly seen to be more prompt than the salivary; there were several occasions when the motor responses were present and the salivary totally absent. No instances were noted in which the motor reflexes were absent after irradiation. It seems therefore that the stimuli must have reached the cortex, in order to produce this biphasic motor response—toward the stimulus, then toward the food pan. A zero salivary reading for the conditioned reflex to rotating feathers, for example, cannot be taken under such circumstances as a sign of absence of excitation of a possible cortical "center" for this stimulus, since both phases of the motor reflex were outspoken.

The dog was killed on July 22, six weeks after exposure to the roentgen rays.

Dog 4.—This was an active animal, aggressive toward other dogs but very friendly toward people. He developed his initial conditioned reflexes fairly promptly and was always eager to "work" on the stand. When presented with a metronome stimulus with beats 120 times a minute followed by food, and then with one beating 60 times a minute without food, he quickly learned the differentiation. He gave normally large salivary reflexes to the former and little or no secretion to the latter. The reflexes to identical stimuli varied widely, so that exact quantitative work was hardly possible. From our experience with this dog, he may be classed as one of balanced type, leaning somewhat in the excitable direction. For a month prior to irradiation he worked in another series of experiments, but with the same daily schedule of stimuli and timing as was used in these experiments. The reflexes recorded during that month serve as the standard of comparison for the after-effects of irradiation.

On Dec. 17, 1930, 5 cc. of a 2 per cent solution of morphine was given subcutaneously and a little over 200 cc. of a saturated solution of chloralose (1.2 Gm.) intravenously for anesthesia. He was then irradiated through five portals of entry centering on the occipital part of the brain, the first three for an hour each, and the last two for forty-five minutes each. The diameter of the localizator was 2 cm., tension 150 kilowats, current 4 milliamperes, distance to skin 25 cm. and filters 0.5 mm. zinc and 3 mm. aluminum, giving a total of 18 human erythema doses at the surface.

The record of the conditioned and unconditioned reflexes appears in figure 2. On the day after irradiation the dog was somewhat unsteady and appeared weak, but ate promptly from the food pans in the chamber. On the second day he behaved quite as usual and experiments were begun again. Then on the fourth

day the conditioned reflex rose slightly above the previous maximal, but only with the first stimulus in the daily series and only for a couple of days, while at the same time the unconditioned secretion became definitely larger than the normal maximum and remained so for five days. From the ninth to the fourteenth day there were three zero readings to light, and then, two weeks after irradiation, the unconditioned reflex dropped a little below the normal minimum. The size of the successive conditioned reflexes also became smaller, so that the last on the list (to metronome) was often below the previous minimum. The first sign of epilation was noticed on the nineteenth day after irradiation. As in the other dogs, this also appeared at the place where cement had been used on the hair to keep the rubber tubing of the balloon in place on the head. By this time the last daily stimulus (metronome) brought out a reflex that was definitely below normal limits each day. Soon the next to last (tone) dropped intermittently below minimum, and later, four weeks after irradiation, the reflex to light in third place on the list always gave small readings, often below the normal minimum, occasionally zero.

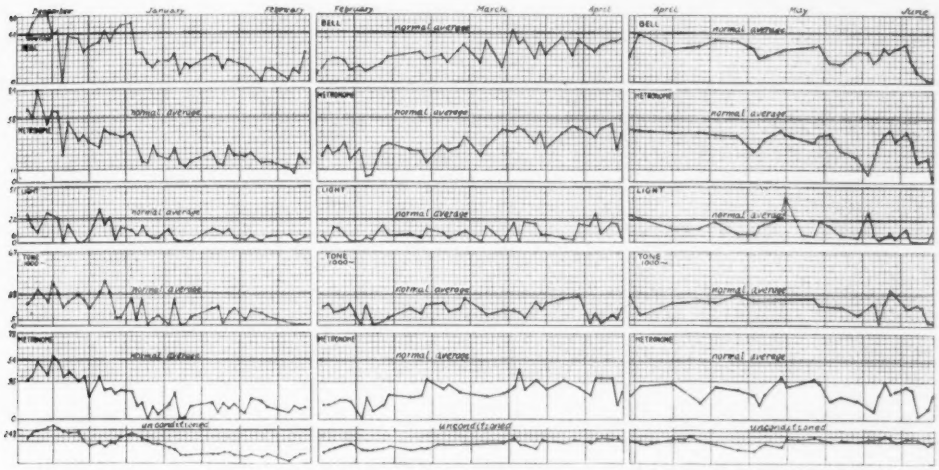

Fig. 2.—Record of the conditioned and unconditioned reflexes in dog 4.

At this time, a month after irradiation, an appreciable drop was noted in the amount of unconditioned salivation; this progressed steadily to a low point thirty-two days after exposure to the roentgen rays. Further, it took much longer to finish his pans of food and the behavior of the animal was quieter, but he shook and scratched himself a great deal, as though subject to a general pruritus. A dry skin was the only sign observed by way of explanation. Five weeks after irradiation, epilation was diffuse over the back of the head and adjacent part of the neck. The sites of the portals of entry were reddened and presented some serous exudation, which soon dried, leaving crusts which in turn disappeared in the course of a week or two. The hair surrounding the area of epilation gradually turned from black to gray. After the low point in conditioned and unconditioned reflexes just mentioned, there was a slight rise in both, lasting about a week, and then, six weeks after the irradiation, both sets of reflexes began to drop again. A second low point was reached seven weeks after irradiation. The reflex to tone gave a zero reading for several days, that to light was usually present but very small, and the rest of the conditioned reflexes were much reduced. The average

unconditioned reflex on the lowest day with reliable data was 37 per cent of the average before irradiation. However, during that period the exact values of the conditioned and unconditioned reflexes were not always significant. The dog would continually shake himself when on the stand, often did not want to start work, and on two days refused food. Afterward, all reflexes began to rise again. Only the last conditioned stimulus in the daily series (metronome) produced salivary responses consistently smaller than the normal minimum for a protracted time. Light gave several, and tone a few, sporadic low readings. The unconditioned secretion rose quite steadily from day to day. On March 3, almost eleven weeks after irradiation, all conditioned reflexes reached normal limits again, but they did not all remain there, and the accompanying unconditioned salivation was still below the normal minimum. The light stimulus continued to bring out reflexes of variable size—never high, often low or subnormal—and occasionally there was total absence of a conditioned reflex. Reflexes with the last daily stimulus (metronome) also fluctuated a little above and below normal. On March 19, thirteen weeks after irradiation, the unconditioned salivary secretion came back to normal, dropped again for five days, and then returned to remain for the most part within the normal zone. On the whole, there was some improvement in the dog's general appearance; he was more alert, ate more rapidly, and scratched and shook himself less, but on March 27, he refused food altogether during an experiment. From the fourteenth to the twenty-first week after irradiation, the conditioned and unconditioned reflexes and the behavior of the animal were approximately normal. During this period only two unusual tendencies appeared: Following the light stimulus the size of the salivary response showed considerable variation from day to day, with occasional subnormal readings, and a distinct decrease in the size of the reflexes during a single day's experiment was rather frequently noted, so that the first two stimuli would produce a relatively large and the last two or three a relatively small amount of salivary secretion.

The last stage in the history dates from the fifth month after exposure to the roentgen rays. On May 15, some ataxia was noticed—"like an animal after narcosis." Within a week there were periods of apparent weakness; although ready to eat, the dog could not get up on to the stand as usual. Then there was a rather rapid change. He lost all former alertness, fatigued readily, would spread the forelegs insecurely apart when shaking and often stood on the back of a forepaw without attempting to get the pad down on to the floor; on going up and down stairs the feet would frequently undershoot and occasionally overshoot the next step, and on turning around the paws would at times slide laterally so that he would drop down into a lying position. This condition varied somewhat from day to day At this stage, Professor Pavlov commented that he had seen similar phenomena in dogs after removal of large parts of the cortex and he thought that the damage in this dog was probably diffuse. During this period the conditioned reflex to light was variable, never high, often below the normal minimum. The last reflex in the daily series (metronome) was also variable and usually subnormal in size. Otherwise the reflexes remained without essential change until June 5, twenty-four weeks after irradiation. From then on, the response to light gave zero readings, with the exception of one experiment on June 9 and the final experiment with conditioned reflexes on June 11, when the dog became too weak to work. During these days the other conditioned reflexes also dropped irregularly to very low values. The unconditioned salivary secretion remained within normal limits as long as the dog ate properly during the experiments. From June 5 on, deterioration in behavior was also rapid; there was little or no recognition of the presence of people or of other dogs; there were periods of whining; occasionally urine would be passed in the work chamber or in the adjoining room, which had

never occurred with this dog before, and although it was not cold weather there was a great deal of shivering. It was noticed on about June 13 that vision was impaired. When roused from lying down, curled up on the floor, he would circle around and around, always in clockwise direction, often bumping up against objects in the room and occasionally giving a whine when he did so. That vision was greatly impaired while smell, touch and hearing were at least relatively well retained became more and more obvious. In an examination of the eyegrounds by Dr. Cheshkov on June 16, the optic disks were reported as normal. Food was more often refused than eaten. At times there was vomiting. Defecation became semifluid during the last few days. The dog grew almost totally unresponsive to people. The body weight dropped 1.7 Kg. in the last two weeks of life, but there was no abnormality in temperature, pulse or respiratory rate.

On June 20, the dog was killed, three days more than six months from the time of irradiation.

HISTOLOGIC OBSERVATIONS

Dog 1.—The architecture in the cerebrum and cerebellum was undisturbed. The meninges and blood vessels showed no changes. The ganglion cells stained rather poorly by the Nissl method (formaldehyde fixation); their nuclei were well preserved; the tigroid bodies were well represented, especially in the larger nerve cells, and there was no change in their fibrillary structure. No dropping out of axis cylinders was evident and no degenerated forms of axis cylinders were to be seen. The glia was normal. Large amounts of lipoids were present in places in the adventitial cells of the large and small blood vessels of the gray and white substance and in the capillaries, usually in large droplets, often enclosed in cells with vacuolated protoplasm and pyknotic nuclei. The nerve and glia cells contained no lipoid.

In two submaxillary lymph glands, the parenchyma was reduced, the lymph sinuses were widened, the reticulo-endothelial tissue was increased, and only a few small lymph follicles were present. There was marked perivascular sclerosis.

Dog 2.—The pia and large blood vessels in the gray and white substance were everywhere thickly infiltrated with lymphocytes, plasma cells and polyblasts. Capillaries and precapillaries were practically free from cellular infiltration. The cellular and fibrillar structures of the nerve parenchyma were relatively little altered. Neither ganglion nor glia cells contained appreciable amounts of lipoids. The latter showed a slight increase in the neighborhood of many of the infiltrated blood vessels in the white substance; syncytial glial groups were found only here and there, particularly in the thalamus. In the cerebral cortex isolated rod cells were seen in places. The occurrence of lipoids in the intracerebral blood vessels was similar to that in dog 1, only quantitatively somewhat less.

There was slight perivascular infiltration in places in the submaxillary glands. The parotid glands showed rather marked diffuse infiltration of the interstitial tissue with round cells and plasma cells, and an increase in interlobular connective tissue, but no appreciable change in the parenchyma.

Dog 3.—The meninges had slight fibrous thickening and contained scanty cellular infiltration (lymphocytes, polyblasts and occasional plasma cells). Many of the larger blood vessels in the thalamus, striatum and cerebral and cerebellar white substance, and in isolated places in the cerebral cortex, showed infiltration of varying density with similar cells. A pronounced glial reaction was found only in the neighborhood of a few densely infiltrated blood vessels in the thalamus. The capillaries and precapillaries were free from infiltration, but there were a slight increase of cells in their walls and definite signs of regressive changes in the endothelial cells (slight shrinking of the nucleus and vacuolization of the

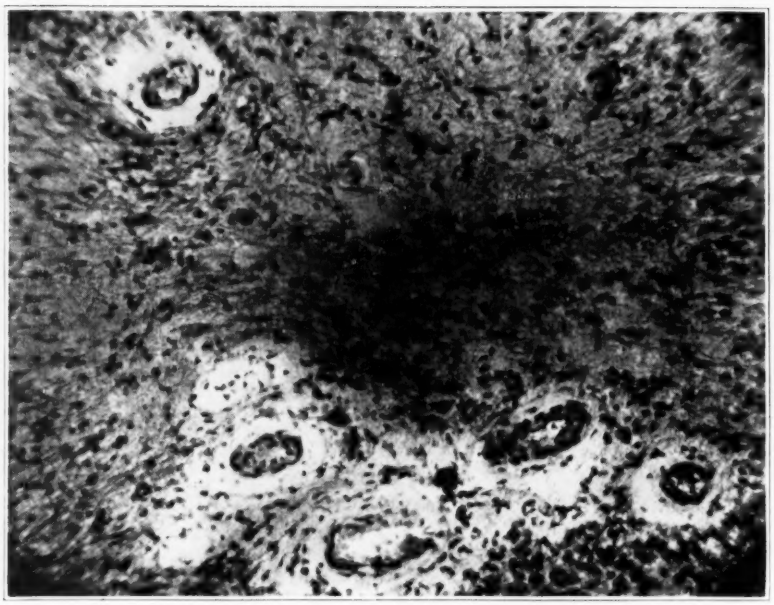

Fig. 3 (dog 4).—A group of blood vessels with hyaline degeneration in the region of the hypothalamus.

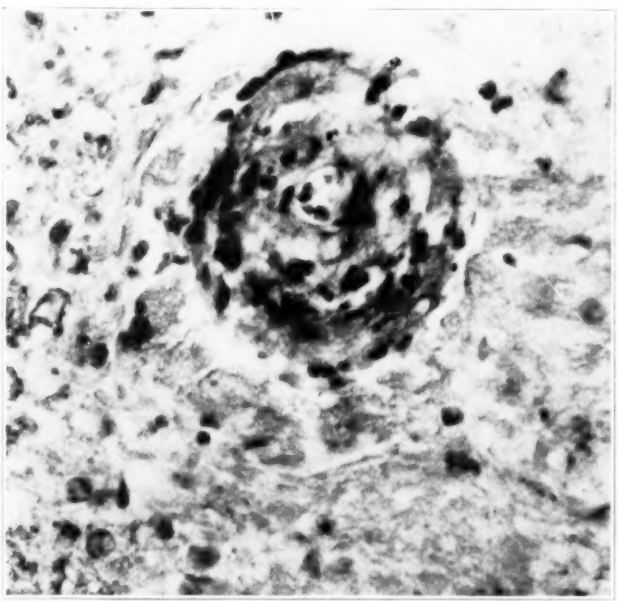

Fig. 4.—Small artery from the hypothalamus showing marked hypertrophy of the intima and a high degree of narrowing of the lumen, vacuolization of the intima and a few polymorphonuclear leukocytes. Active tissue reaction in the vicinity of the vessel.

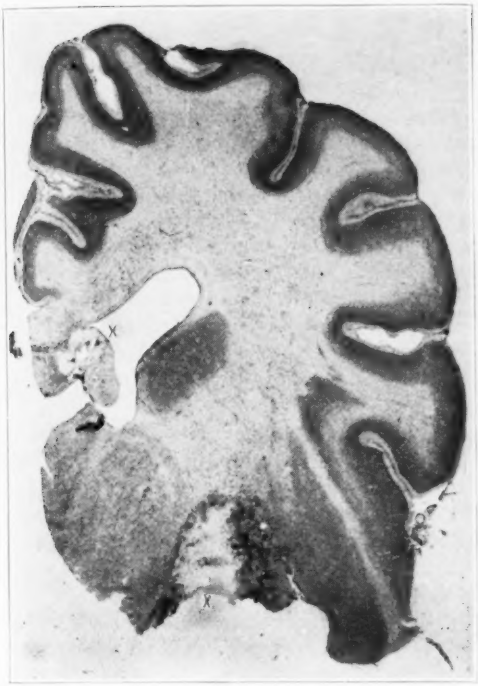

Fig. 5 (dog 4).—Frontal section through cerebral hemisphere. Nissl stain. At *x*, two large focal necroses are seen.

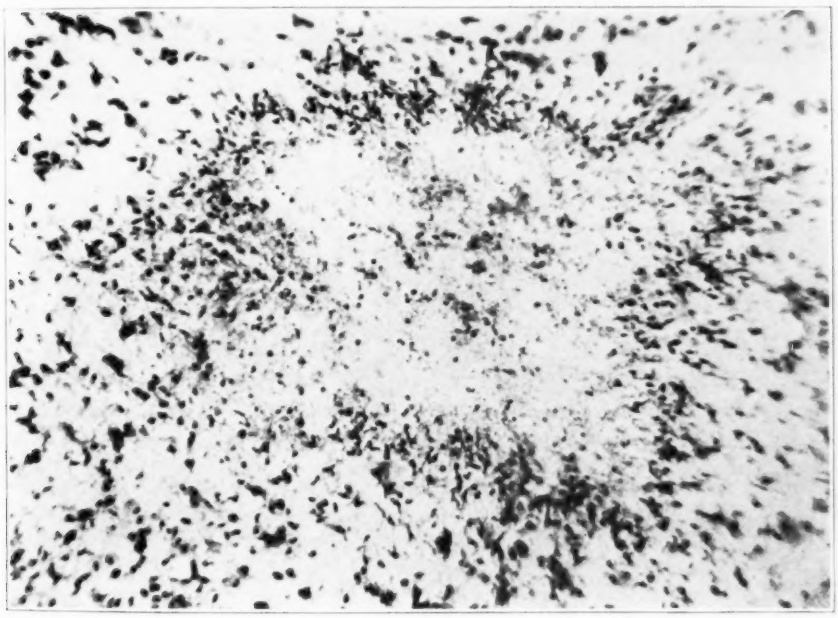

Fig. 6 (dog 4).—Small area of necrosis at the medial tip of the globus pallidus. The space within the necrotic area has broken down into detritus. A wreathlike growth of rod-shaped glia cells are seen around the border of the necrosis. Nissl stain.

protoplasm). No significant damage was evident in the nerve parenchyma; in the large ganglion cells in the cortex the tigroid bodies were well represented and there were only occasionally a few fat granules; there was no difference between the occipital and frontal regions. In many of the intracerebral blood vessels, of all sizes, the adventitial cells as well as the mobile cells in the lymph spaces of the blood vessel walls contained large amounts of lipoids in large droplets. The meninges also contained much fat. It was the same sort of condition as in dogs 1 and 2, only the fat-containing cells were more numerous.

The interstitial tissues of the parotid gland were diffusely infiltrated with round cells and plasma cells; in places there was an increase in density with extensive clumps of round cells in evidence. In a few places there was partial sclerosis in the lobules of the gland.

Dog 4.—The meninges had slight fibrous thickening. The architecture of the cerebral and cerebellar cortex was undisturbed, with the exception of a whorl-like arrangement of ganglion cells in one place in the occipital cortex (developmental anomaly?). A few myelin fibers in the lamina zonalis showed degenerative changes. In the chiasma opticum there were some small areas of destruction of myelin, in which the fixed glia cells were densely packed with fat. The ganglion cells in the cerebral cortex contained considerable lipoidal pigment, but all forms of glia cells, which were not increased, contained only little. The larger ganglion cells showed scarcely any change in tigroid bodies; the intracellular fibrils did not stand out clearly, but in the cell processes they were always well preserved. The meninges and blood vessels contained even larger amounts of fat than in dog 3. Capillaries and precapillaries showed outspoken regressive changes in the cells of their walls, even more clearly than in dog 3, i. e., shrunken nuclei, hypochromatosis and vacuolization of protoplasm. In all parts of the brain, but especially in the subcortical ganglia, the arteries and arterioles were thickened and hyalinized to a more or less high degree (fig. 3). Other arteries showed a peculiar form of sclerosis. In these vessels the intima was thickened with signs of degeneration, and the lumen was extensively narrowed (fig. 4). These changes are the same as those described by Jassmann [32a] in ulceration produced by roentgen rays. Around such hyalinized and sclerotic blood vessels there was frequently a rather broad zone free from nerve cells or a zone of myelin sheath destruction. Along the blood vessels of every caliber, including the capillaries, one saw with the use of the tannin-silver method numerous connective tissue fibrils. Frequently there ran from one capillary to another solid fibrillary strands (*cordons unitifs*), often spreading in wide arcs. The most striking pathologic finding consisted of several extensive areas of total necrosis, the location of which could be seen in figure 5. The necrosis in the hypothalamus and capsula interna extended to the inner portion of the globus pallidus and to a part of the optic tract. In the débris there were numerous nuclear fragments. Some smaller areas of necroses were encircled by a wreath of glia cells with a palisade proliferation and many rod forms (fig. 6). In the outer zones of the larger areas there was an active removal of débris (numerous macrophages and granular cells); here, cells in the blood vessel walls and glia cells showed evidence of active proliferation. At the outer border of the hypothalamic necrosis there was an abundant growth of connective tissue fibers, while in the necrosis in the region of the corpus callosum no trace of mesenchymal organization could be made out. The arterioles in the region of the necroses were often hyalinized and sclerotic to an especially high degree. A few blood vessels in the neighborhood were surrounded by an inflammatory coat of lymphocytes, polyblasts and numerous plasma cells. The blood vessels within these areas were necrotic and their structure was

32a. Jassmann, cited by Wetterer, J.: Handbuch der Röntgen- und Radiumtherapie, Leipzig, Keim und Nemnich, 1922, vol. 1, p. 340.

no longer recognizable. In the pons, numerous plasma cells were found along some of the larger blood vessels, and a few along the capillaries. Evidences of degeneration in the nerve parenchyma or reaction of the glial tissue were not seen in the pons.

There were slight interstitial round cell infiltration and extensive atrophy in the glandular lobules of the submaxillary gland, but no changes in the parotid.

COMMENT ON PHYSIOLOGIC RESULTS

Professor Nemenov [33] was the first to apply conditioned reflexes to the study of roentgen action on dogs' brains. Unreported experiments by Nemenov and Kupalov showed that the conditioned reflexes would usually be more or less changed after exposure of the heads of dogs to 3 or 4 erythema doses. In order to get very sharp results, the four dogs presented here were exposed to a higher dosage—from 18 to 20 erythema doses. The subsequent behavior and conditioned reflexes of these animals seemed to pass through four stages.

For a period lasting from one to three weeks after irradiation, the picture varied from dog to dog. It took a day or two for the animals to recover from the trauma attending the irradiation. Then their behavior appeared quite normal, but the conditioned reflexes showed individual differences. Previous observations had established the physiologic "type" or constitution of each of these dogs (Pavlov). Dog 2 represented the excited type and gave supernormal conditioned reflexes during the first two weeks after irradiation. Dog 4 was balanced but leaning in the excitable direction and had high normal reflexes during this same stage. Dog 3 was balanced but leaning toward the inhibited type and showed somewhat subnormal reflexes. Dog 1 was strongly inhibited, and most of his conditioned reflexes gave zero readings. Accordingly, just after irradiation some increase or decrease of excitability of cortical function occurred and these variations fell in line with the inherent physiologic constitution of the dog.

The second stage began in the second or third week and continued to the fifth week or somewhat longer. The general behavior might appear normal, but a lowering of the usual spontaneous activity was sometimes noted. Epilation occurred with sufficient roentgen dosage. Conditioned reflexes always dropped to a more or less extent and the uncondition secretion might also decrease. The latter suggested suppression of salivary secretion by action of the roentgen rays directly on the salivary glands. Ceresole [34] established clinically that changes in salivation took place after exposure of the lower part of the face or

33. Nemenov, M.: Ueber die Einwirkung der Roentgenbestrahlung des Gehirns auf die bedingten Reflexe, Acta radiol. (supp. 3), 1928, pt. 2, p. 169.

34. Ceresole, G.: Arch. d'électric. méd. **20-21**:304, 1912.

neck to the x-rays. Jüngling,[35] Salis,[36] Schmidt[37] and Tsuzuki[38] have described temporary histologic changes in irradiated salivary glands. Case and Boldyreff[39] used the method of conditioned and unconditioned reflexes to show that salivation would drop to a low point three or four weeks after irradiation and return to normal values in the second to fifth month in dogs that received 450 milliampere minutes of roentgen rays filtered through 1 mm. copper and 1 mm. aluminum directly over the glands. And so, the probability that the salivary reflexes are altered by direct action of the roentgen rays on the glands during this stage is recognized. However, such an effect on the salivary apparatus can hardly be the sole explanation of the low conditioned reflexes, since the unconditioned salivation provides an index of the ability of the glands to secrete, and it did not always fall below normal minimal values. Also, when the unconditioned secretion was decreased, it seldom fell in proportion to the marked drop in the conditioned reflexes. Accordingly, this second stage can be said, with reservation, to be one of more or less reduced cortical excitability.

A third stage began with a return of the conditioned and unconditioned reflexes to their original size. The behavior seemed to be quite normal. The duration of this period cannot be given with certainty since there is only one dog in this series to determine it. However, work with other unreported dogs also gives the impression that a time comes when the natural level of cortical excitability is in no way disturbed and the dogs appear perfectly well.

The fourth stage came some five to six months, or more, after exposure to the roentgen rays. Definite signs of cerebral damage then developed. Of the four dogs reported on here, only the last one was allowed to live long enough to reach this stage. This dog and others observed by Nemenov and Kupalov, as well as those irradiated by Warren and Bishop,[40] of Rochester, N. Y., presented symptoms such as ataxia, impairment of vision, circus movements, sluggish or excited

35. Jüngling, O.: Roentgenbehandlung chirurgischer Krankheiten, Leipzig, S. Hirzel, 1924.

36. Salis, H.: Zu den Roentgenveränderungen nach Bestrahlung der Gland submaxillaris, Strahlentherapie **17**:395, 1924.

37. Schmidt, H.: Kehlkopfgangrän als Roentgenspätschädigung, Virchows Arch. f. path. Anat. **231**:557, 1921.

38. Tsuzuki, M.: Experimental Studies on the Biological Action of Hard Roentgen Rays, Am. J. Roentgenol. **16**:134, 1926.

39. Case, J. T., and Boldyreff, W. N.: A Study of the Influence of High Voltage Roentgen Irradiation on Salivary Secretion in Dogs and Its Effect on the Sensibility of the Buccal Mucosa, Am. J. Roentgenol. **13**:130, 1925.

40. Warren, S. L., and Bishop, F. W.: Personal communications, from the University of Rochester, Rochester, N. Y.

behavior and general deterioration, or merely sudden death without other ascertainable cause. In dog 4, the conditioned reflexes corresponded with the clinical picture, dropping irregularly below normal values and yielding small or absent responses to light during the period when he showed other evidence of becoming blind. The unconditioned salivation was normal. This dog was killed six months after irradiation. The other dogs mentioned died spontaneously, often after weeks or months of disability.

Analysis of the conditioned reflexes in this series of experiments provides evidence of diffuse change in cortical and subcortical function.

In the first place, the center of cross-fire with the roentgen rays was directed at the occipital portion of the head of each dog. Even if considerable scattering of irradiation did occur, the visual centers in the occipital lobes certainly received the heaviest dosage. And yet the conditioned reflexes to visual stimuli were not correspondingly altered, except in the final period in the study with dog 4. That dog then became partially blind, and the cause was proved histologically to have been due to patches of demyelinization in the optic chiasm. The position of the stimulus in the daily series, regardless of its nature, seemed most important. The last on the list was the most affected. Then, all "weak" stimuli suffered—light, tone, tactile stimulation—regardless of the cortical localization of these functions. Accordingly, although the visual part of the cortex was most intensively irradiated, the conditioned reflexes were diffusely affected and did not match the cortical areas of maximal irradiation.

Also, a discrepancy was noted between motor and salivary conditioned reflexes. The motor reflexes consist of two movements: first, toward the conditioned stimulus as soon as it begins, and then to the food pan before the time for it to appear. For the completion of this twofold conditioned reflex the stimuli must reach the cerebral cortex, but not depend on any essential subcortical or vegetative mechanism for the resulting motor responses to take place. On the other hand, the salivary conditioned reflexes also require stimuli to reach the cortex, but the impulses must then be relayed out through the subcortex and vegetative nervous system, which control the salivary secretion. With dog 3, conditioned salivary reflexes were repeatedly noted to be minimal or totally absent when the conditioned motor reflexes were clearly preserved. Dog 1 showed some motor reaction to the conditioned stimuli, while salivation did not occur. Thus, the roentgen action affected those reflexes in which the indicator was under control of the subcortex and vegetative nervous system and spared those which were independent of subcortical control.

Further, during the second stage after irradiation with all four dogs, epilation began at the spot on the head where a little cement was

used on the hair to hold a light rubber tube in place during each experiment. This spot was not always at the site of a portal of entry for the roentgen rays, but was on the side on which the parotid fistula opened on to the cheek. This cheek was subject to daily gentle manipulation in fixing the balloon in place for the collection of saliva. As epilation went on, that same side of the head became completely bare before there was any appreciable falling of hair from the other side. This suggests a vegetative influence of the roentgen rays: Considerable direct evidence of change in the vegetative nervous system under roentgen irradiation has, of course, been reported in the literature by a number of investigators, including Ricker,[41] Swann,[42] Strauss and Rother,[43] Langer,[44] Rütz,[45] Schilling,[46] Meiszel,[47] Zimmern and Chavany[48] and Zimmern, Chailley-Bert and Hickel.[49]

Thus, physiologic evidence indicates that, even when directed at a single part of the central nervous system, the effect of roentgen irradiation was diffuse, that it involved the subcortex as well as the cortex and that there were coincident features pointing toward a vegetative nervous influence.

HISTOLOGIC RESULTS AND PATHOGENIC CONCLUSIONS

In all the animals there is the widespread occurrence of fat in the adventitial cells of the blood vessels, the origin of which is not explained by the other histologic changes, at least in dogs 1 to 3. In them the nerve and glia cells contain practically no lipoid, and the endothelium of the blood vessels, particularly of the capillaries, presents no morphologic changes in dogs 1 and 2. In dog 4, the diffuse degenerative changes of the nerve parenchyma are hardly enough to explain the large quantity of fat in the blood vessels. The finding of fat deserves attention, because Mogilnitzky and Podljaschuk have pointed out the occurrence of fat in the endothelium in irradiated dogs,

41. Ricker, G.: Strahlentherapie **5**:679, 1915.

42. Swann, M. B. R.: A Study of the Immediate Effects of X-Rays on the Functions of Certain Tissues and Organs, Brit. J. Radiol. **29**:195, 1924.

43. Strauss, O., and Rother, J.: Strahlenwirkung auf das vegetative System, Strahlentherapie **18**:37, 1924.

44. Langer, H.: Roentgen Rays and the Autonomic System, Am. J. Roentgenol. **18**:137, 1927.

45. Rütz, A.: Ueber Roentgentiefenbestrahlung und vegetatives Nervensystem, Arch. f. klin. Chir. **145**:663, 1927.

46. Schilling, E.: Die Sensibilisierung des vegetativen Systems durch Buckysche Grenzstrahlen, Ztschr. f. d. ges. exper. Med. **74**:713, 1930.

47. Meiszel, M. N.: Virchows Arch. f. path. Anat. **276**:77, 1930.

48. Zimmern, A., and Chavany, J. A.: J. de radiol. et d'électrol. **14**:433, 1930.

49. Zimmern, A.; Chailley-Bert, P., and Hickel, R.: Expériences pour déterminer l'action des rayons de roentgen sur le système neurovégétatif du chien, Compt. rend. Soc. de biol. **103**:494, 1930.

and the sensitivity of the capillary endothelium to irradiation has recently been emphasized by Marburg and Sgalitzer. For this reason, control examinations were undertaken on the brains of dogs none of which had been subjected to roentgen irradiation. In all of them fat was found in the blood vessels just as in the irradiated dogs. The fat in two of the normal animals was even more abundant than in the irradiated dogs 1 and 2. We have obtained from the literature no explanation of this phenomenon. Perhaps in dogs it is not strictly normal, but it is nevertheless a commonplace observation, which can be attributed neither to the irradiation nor to the narcotic agents used with it. At best, the irradiation could produce only an increased amount of fat, for which the changes in dog 4 speak.

Accordingly, none of the demonstrable changes in the brain of dog 1 can be referred to the irradiation.

In dog 2, the results of the examination can be summarized in the histologic diagnosis of "acute meningo-encephalitis with severe infiltration and relatively slight parenchymatous damage." The changes resemble those of distemper (Staupe).

In dog 3, there is a similar diffuse encephalitis but it is less intense. The changes in the glial tissue are slight. In contrast to the observations on dog 2, there are slight degenerative changes in the walls of capillaries and precapillaries, with no lymphocytes or plasma cells as in dog 2. This is noteworthy in view of the changes in dog 4, which provide the greatest difficulties in explaining the pathogenesis.

It is striking that the severe meningo-encephalitis in dog 2, and the encephalitis in dog 3, exhibited scarcely any clinical expression in spite of close observation. This discrepancy had already been noticed in 1912 by Cerletti,[50] in his observations on dogs with distemper. It is possible that the inflammatory process, the pathogenesis of which will be discussed later, influenced the changes in the conditioned reflexes, which were observed some weeks after irradiation. The cerebral symptoms in dog 4 find their explanation in the lesions in the nerve parenchyma, which were visible even macroscopically. In particular, the severe impairment of vision with normal eyegrounds is traceable to the lesions in the chiasm and in the optic tract, which, according to the histologic changes, could not have occurred until shortly before death.

In dog 4, the lesions were: (1) slight degenerative changes of diffuse distribution in cerebral gray and white matter (increased fat in the ganglion cells and numerous fat-laden fixed glia cells in the white substance); (2) several small, recent areas of destruction in the chiasm;

50. Cerletti, U.: Ueber verschiedene Encephalitis- und Myelitisformen bei ein Staupe erkrankten Hunden, Ztschr. f. d. ges. Neurol. u. Psychiat. (O.) **9**:525, 1912.

(3) several large and small fresh areas of necrosis, of different age, in the hypothalamus and the middle section of the corpus callosum; (4) regressive changes of the capillaries and precapillaries; (5) marked hyaline and sclerotic degeneration of the arterioles in all parts of the brain, and (6) inflammatory changes in the form of slight infiltration of the blood vessels in the subcortical parts of the brain (chiefly midbrain and interbrain) with the presence of plasma cells along the capillaries.

This is not a so-called symptomatic inflammation (Spielmeyer), as the relatively mild degree of infiltration and the existence of necroses might suggest. The occurrence of plasma cell infiltrations in the pons far from the necrotic areas points to a primary inflammation. Whether we were dealing with an infection is difficult to state. The clinical picture gives quite as little that is definite in this respect. Only in dog 3 was there any behavior in the past that could be taken in the light of the changes in the brain as an expression of an inflammation of the brain. It is possible that the high roentgen dosage reduced the power of resistance of the brain to infections; unpublished observations by Nemenov and Kupalov and by Warren and Bishop suggest this possibility, as several irradiated dogs after several months presented severe cerebral symptoms and died. The lesions in dog 4 may, as will be seen later, be due purely to irradiation. Whether or not irradiation alone can excite an inflammatory reaction in the vascular system of the brain as a late result can be verified only after special precautions have been taken with more material. However, it is certainly striking that the three dogs which lived for a longer period after irradiation all showed inflammatory changes in the brain, although they were kept separated while alive, so that an infection from one to the other was improbable. Rodet, Bertin-Sans and Beier recorded similar observations; there are few observations in the literature over so long a period as is described in dog 4. On the other hand, changes in the vascular system similar to those we found in dogs 3 and 4 have been described in the brains of dogs that were examined histologically a shorter time after irradiation. Mogilnitzky and Podljaschuk, in particular, and recently Marburg and Sgalitzer have pointed to the tendency of the smallest blood vessels to react to irradiation by regressive changes of their endothelium. In dog 3 such changes were definite, and in dog 4 very pronounced; in the latter the process also went on to a diffuse activity of the cellular glia in the white substance, especially marked around the blood vessels, without any trace of inflammation in the neighborhood.

The high grade hyaline degeneration and obliterating sclerosis of the larger vessels are described here as a new change in the brain which is especially intensive in the subcortical ganglia. As in human arterio-

sclerosis, there is here evidence of perivascular parenchymatous atrophy (zones free from ganglion cells) and the focal necroses as well should be attributed to this vascular degeneration. Although the vascular structure is no longer recognizable inside the necrosis, yet one can still see in the necrotic detritus that the centers of the necroses are founded on larger blood vessels. This change and the sharp border of the necrosis which occupies more or less the region of a larger blood vessel make it rather certain that it depends on vascular conditions. Moreover, the small degenerative patches as seen in figure 6 are without doubt of vascular origin. Finally, the hyaline and sclerotic degeneration of the blood vessels can accordingly be made responsible for the necrosis in all probability. There is no evidence that the changes of the vessels could be produced in some way by the coexistent inflammation, for it is found throughout the brain, even where no trace of inflammation exists and moreover where there is nothing else to indicate that an inflammatory process had previously played a part. Still, it cannot be denied that the existence of inflammation as a factor in the constellation could have played some rôle in the production of the necrosis; even its influence on the vascular tonus cannot be taken as a matter of indifference in regard to the severe changes of the blood vessels. However, in view of the obvious vascular factor, the inflammation cannot in itself be made responsible for the production of the necroses. This would be the less justified since in many necroses, such as that which is reproduced in figure 6, inflammatory changes are not to be seen in the necrotic areas or in their immediate neighborhood. Also, the slight diffuse degenerative changes of the nerve parenchyma in the gray and white substance and especially that in the optic chiasm are probably to be explained by the damage to the large and small blood vessels. Direct injury of the nerve parenchyma by irradiation is not probable in view of the focal destruction of fibers in the chiasm and of the nature of the diffuse degenerative changes which vary in different places. Moreover, the fact that the lesions were no less pronounced throughout the nonirradiated frontal region speaks against it.

Résumé.—The clinical literature states that small therapeutic doses of roentgen irradiation do no damage to the adult central nervous system itself and have practically no effect on its function. If any, the effect consists merely of a slight temporary depression of excitability. Irradiation may produce some changes in blood vessels on intense or repeated administration in the clinic, and it may temporarily reduce the secretion of cerebrospinal fluid. On the other hand, there is considerable evidence of roentgen action on the vegetative nervous system.

Conditioned reflexes were first applied to the study of a roentgen effect on the central nervous system by Prof. M. I. Nemenov.

The results of exposing the occipital region of the heads of four adult dogs to high dosage of roentgen rays (from 18 to 20 erythema doses) are reported in this paper. Studies with conditioned reflexes showed that:

1. During the first stage, lasting from one to three weeks after exposure, there was considerable individual difference in the reactions. This appeared to be constitutional and conformed to the "physiologic type" of dog (Pavlov) as determined before irradiation, chiefly by means of conditioned reflexes.

2. During the second stage, from about the second to the twelfth week or longer, the conditioned reflexes were always below the normal range. Unconditioned reflexes were often low as well, suggesting direct roentgen action on the salivary glands. Signs of some vegetative disturbance might also appear. Therefore, in this period, the conditioned reflexes had limited significance, but probably indicated more or less depression of cortical excitability.

3. A third stage of apparently normal salivary reflexes and behavior followed recovery from the second stage.

4. A fourth stage occurred in the one dog in this series which was allowed to survive for a sufficiently long time. Marked changes appeared, such as ataxia, loss of vigor and clockwise circling around, beginning five months after irradiation; by the sixth month there were gross impairment of vision and pronounced deterioration of behavior. Severe symptoms of lesions in the central nervous system were also observed several months after exposure to high doses of roentgen rays in other adult dogs, not reported on here.

The results of histologic examination showed that intensive irradiation in dog 1 led in the course of one week to no morphologically recognizable damage to the brain. From the standpoint of significance of pathology, dog 2 was thrown out of consideration on account of the extraordinarily intense inflammatory changes. With equal roentgen dosage in dog 3, at the end of six weeks, in addition to signs of inflammation of uncertain significance there were definite changes on the part of the cells in the walls of the precapillaries and capillaries (slight increase of adventitial and endothelial cells with subsequent regressive alteration). Six months after exposure to slightly smaller roentgen dosage in dog 4, the degenerative changes in the capillaries and precapillaries had gone on, as a further late result, to severe hyaline degeneration and obliterating sclerosis of arterioles, to the account of which can be ascribed several extensive necroses in the brain.

The late results from irradiation in the form of changes in the precapillaries and capillaries in the brain agree with the statements in the literature and speak for their general acceptibility. In addition, this

investigation shows that after intensive irradiation severe damage to the larger vessels in the brain also enters in. Experiments with a larger group of animals will be needed to settle the general validity of the degeneration of the large vessels and the appearance of necroses in their wake, as well as whether or not irradiation alone can call out inflammatory changes. However, that very serious late injuries are not unusual as a result of irradiation is shown by the observations on the other dogs already mentioned, which unfortunately could not be submitted to histologic examination for various reasons.

Roentgen rays may alter the function of the central nervous system, but their action does not seem to be primarily on the cells of the cerebral cortex. After a high dosage in adult dogs there may be some lowering of excitability of cortical cells, as determined by conditioned reflexes, but this appears to be secondary to changes in blood supply. Even when directed at a single area of the brain, irradiation gives a diffuse physiologic and pathologic effect, involving the subcortex as well as the cortex, and probably the vegetative nervous system as well. Accordingly, in spite of some photographic evidence that the physical action of the roentgen rays can be fairly sharply localized inside the skull, there is little hope of selecting one spot in the brain for cross-fire with a small beam and of increasing the vascular permeability at that spot by irradiation, and then treating through the blood stream so that the desired area will get relatively more medication than other parts of the brain.

SUMMARY

Four adult dogs received heavy dosage of roentgen rays on the occipital part of their heads. Physiologic variations followed irradiation, as determined by conditioned reflexes. Histologic examination showed diffusely scattered degenerative changes in the precapillaries and capillaries of the brain six weeks after irradiation. One dog was allowed to live for six months after irradiation and in the fifth month there developed signs of diffuse damage to the functions of the cortex and subcortex. At autopsy the changes in the precapillaries, capillaries and larger vessels of the brain had progressed and there were marked hyaline degeneration and obliterating sclerosis of arterioles with numerous resulting areas of complete and incomplete necrosis.

CHROMATOLYSIS OF EFFERENT NEURONS

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Review of the literature relative to experimental peripheral injury to the nerves reveals many interesting results, interpretations and contentions, particularly concerning the effects produced on the body of the nerve cell. The subsequent changes in the neurocyte are exceedingly variable and present histologic pictures varying from one extreme to the other, namely, from that of no apparent change at all, to that of complete disintegration and disappearance of the cell.

These alterations or lack of alterations are dependent on at least four factors: first, the type and the age of the animal used; second, the distance from the central nervous system at which the nerve is severed, ligated or otherwise injured; third, the interval that is permitted to elapse between the time of operation on the nerve and that of removal and fixation of the tissue of the central nervous system, and, fourth, the histologic and functional type of neuron.

The effects of peripheral nerve section result, in most instances, in profound changes in the nerve cell body, expressed primarily as alteration of the normal Nissl bodies or chromophilic granules of the cytoplasm. As phenomena of secondary significance, because of the inconstancy of their occurrence, there are changes in the size of the cell body and in the position of the nucleus within it. The modification of the Nissl bodies is referred to by the well known term "chromatolysis," signifying a fragmentation or dissolution of the chromophilic granules, but not necessarily implying their complete or almost complete disappearance from the cell.

In this article no attempt will be made to review and evaluate the results of the numerous investigators in this field of experimentation or to present an extensive bibliography. The papers of Bucy [1] and of Nicholson [2] contain complete bibliographies to which the reader may refer. In this article, reference will be made only to papers examined and read which have an immediate bearing on its intended content. The

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From the Department of Anatomy, University of Wisconsin.

1. Bucy, P. C.: Studies in Degeneration of Peripheral Nerves, J. Comp. Neurol. **45**:129 (April) 1928.

2. Nicholson, F. M.: The Change in Amount and Distribution of the Iron-Containing Proteins of Nerve Cells Following Injury to Their Axones, J. Comp. Neurol. **36**:37 (Oct.) 1923.

primary purpose in the present paper is to describe and illustrate with the accompanying photomicrographs the modifications that the efferent neurons of certain peripheral nerves undergo exemplifying the factors already mentioned.

TYPES OF ANIMALS USED AND TECHNIC

In this work large, healthy rabbits and rhesus monkeys of average size were used. In the rabbits, various nerves of the brachial plexus were divided in the axillary fossa; the vagus and hypoglossal nerves were cut in the neck, each at approximately the same distance from the brain, and section or evulsion of the oculomotor nerve was done within the orbit. In all cases a part of the nerve trunk was removed to eliminate the possibility of union. In the monkeys, the following operations were performed, each in a different animal: unilateral section of the median nerve in the axillary fossa; unilateral section of the radial nerve in the same location, and intradural section of the ventral root of the seventh cervical nerve. All of the operations were performed under aseptic conditions, and none was complicated by infection. The anesthetic varied. In some cases ether alone was used; in others, intraperitoneal injection of a barbiturate, usually pentobarbital sodium, and in others, a combination of ether and a barbiturate.

After a time the animals were killed. The rabbits were killed by air embolism, 10 cc. of air being injected into a vein of the ear; the animal was then bled. The monkeys were killed by bleeding following light etherization. Removal of the desired part of the central nervous system was effected as rapidly as possible after the death of the animal and fixed in 95 per cent alcohol for twenty-four hours or longer, dehydrated in absolute alcohol, cleared in oil of cedar and embedded in paraffin. Tissue from some of the animals was embedded in celloidin according to the usual technic. The paraffin sections were cut at 10 microns to insure a complete series; the celloidin sections were cut at 15 microns. The latter were also kept in serial order. All of the material was stained in a 0.5 per cent aqueous solution of toluidine blue. Hopkins [3] made a study of the appearance of the Nissl substance following variations in fixation. In his experiments he used the ventral gray column cells of the white rat. As a result of his investigations he concluded that the clarity of the Nissl bodies varies with the fixative used, and that fixation in 95 per cent alcohol does not produce cleancut Nissl substance. The experience in the laboratory in which my study was made has been rather different, and alcohol fixation has been satisfactory.

REVIEW OF THE LITERATURE

In summarizing the results and interpretations of the earlier investigators on changes in the nerve cell bodies subsequent to peripheral nerve injury, I cannot improve on the description given in a paper by Warrington,[4] which I quote verbatim:

That a relation exists between the structure of a nerve cell and the integrity of its axon is shown by evidence of three kinds.

3. Hopkins, A. E.: The Appearance of Nissl Substance in Nerve Cells Following Variations in Fixation, Anat. Rec. **28**:157 (July) 1924.

4. Warrington, W. B.: On the Structural Alterations Observed in Nerve Cells, J. Physiol. **23**:112, 1898.

(I) In newly-born animals Gudden long ago showed that section of a nerve trunk gives rise to complete disappearance or perhaps an arrest of development of the cells of origin.

(II) In adult animals a somewhat similar condition has been noticed if a long time has elapsed since the occurrence of the lesion.

Forel in 1887 cut the facial nerve in two guinea-pigs at the stylomastoid foramen and allowed the animals to live 262 days and 141 days respectively; in both cases he found marked diminution in the number and size of the cells in the side of the lesion.

Darkschewitsch in 1892 also divided the facial and hypoglossal nerves and after six weeks found changes in the nuclei of origin, the cells being diminished in number, atrophied and shrunken. The changes found in the cord after amputations have already been alluded to and evidence adduced to show that one factor concerned in their production is the cutting off of the afferent impulses which normally innervate the anterior cornual cells by means of the reflex collaterals of the posterior roots.

(III) Nissl in 1892 introduced his method of staining nerve cells by methylene blue, and stated that in so short a period as 24 hours after division of the trunk of the facial nerve an alteration in structure could be found in the corresponding nucleus. The changes described by Nissl may be thus summarized: After 24 hours the blue bodies may be seen to undergo an alteration at one point in the cell which consists in a loss of their distinctive shape and arrangement and a dispersion over the body of the cell. In from two to three days this change spreads all over the cell. The Nissl bodies become paler and ultimately take the appearance of minute specks of colouring matter. On the fourth day the whole cell is swollen and more globular and the processes are homogeneous. On the sixth day the cells appear as if uniformly covered over with the finest coloured particles and the processes have disappeared. The nucleus passes toward the periphery and finally disappears. The change takes place with greater rapidity in some cells than others, but at the eighteenth day all the cells in the nucleus are thus broken up.

Warrington's own work has been carried out, and observations made on the condition of the spinal cord after section of an anterior root, of the oculomotor nucleus after intracranial division of the third nerve and of the facial nucleus after division of that nerve at the stylomastoid foramen.

ALTERATIONS IN THE NERVE CELL BODY

Alterations Depending on the Age and Type of Animal Used.—Apparently, the younger the animals, the more susceptible are the nerve cells to injury. As already stated, Warrington referred to Gudden as showing that in newly born animals section of a nerve trunk gives rise to complete disappearance or perhaps an arrest of development of the cells of origin. I do not have any first hand information or evidence on this point.

Relative to the type of animal utilized there are several interesting features. Goering,[5] experimenting on albino rats, found and described

5. Goering, J. H.: An Experimental Analysis of the Motor Cell Columns in the Cervical Enlargement of the Spinal Cord in the Albino Rat, J. Comp. Neurol. **46**:125 (Aug.) 1928.

definite chromatolytic changes in the cells of the ventral gray column of the cervical portion of the spinal cord from ten to twelve days after section of branches of the brachial plexus in the axillary fossa. His illustrative drawing shows the chromatolytic cell to be much smaller than the normal cell. This may be uniformly true for the somatic motor cells of the white rat, but it is certainly not always the case in chromatolytic cells in general, as I shall show later. Section of corresponding nerves in the rabbit does not result in changes in the cell bodies of the ventral gray columns of the spinal cord in the cervical region after an interval of from eight to ten days. It has been stated by other investigators that section of a peripheral spinal nerve results in no apparent change in the cells of the cord. In the monkey, on the other hand, section of the radial and of the median nerve in the axillary fossa results in definite chromatolytic changes in the ventral gray column cells after an interval of from a week to ten days (fig. 2).

Alterations Depending on Distance from Central Nervous System at Which Nerve Is Severed or Injured.—The degree of damage produced within the nerve cell body is in direct ratio to the proximity of the injury to the central nervous system. If a peripheral nerve is cut at some distance from its point of central attachment, the cells will, in time, completely recover. If the injury is near the central nervous system the cells will have become so affected that they are wholly unable to recover and will die. The differences in the histologic pictures are striking. Section of a somatic motor nerve, such as the hypoglossal, in the rabbit results in changes in the cells of the hypoglossal nucleus as illustrated in figure 5. This illustration shows the condition of the cells nine days after section of the hypoglossal nerve in the neck in the region of the hyoid bone. Figure 7 illustrates the changes in the cell bodies of the somatic motor nucleus of the oculomotor nerve of the rabbit eight days after evulsion of the nerve from the brain. In the animal from a section of which this photograph was made, the oculomotor nerve was located in the orbit and carefully pulled from its attachment to the brain. Postmortem examination verified this fact. The details of difference in appearance of the cells dependent on the location of the injury are described in the legends accompanying the illustrations. I have not yet followed the changes later than the eighth day after evulsion of the nerve, but in view of the extensive injury to the cells it is highly improbable that they will be able to recover and resume their normal appearance.

Alterations Depending on Interval Elapsing Between Time of Operation on Nerve and Removal and Fixation of Tissue of Central Nervous System.—As previously stated, Nissl in 1892 showed that the cells of the facial nucleus underwent an alteration of structure within twenty-four hours after section of the facial nerve. The subsequent changes which he observed in the cells have already been described.

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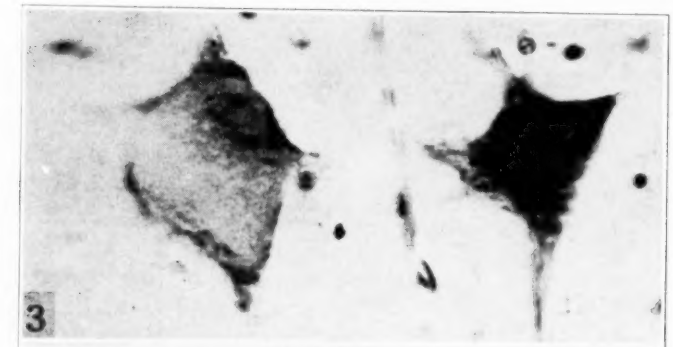
Fig. 1.—Normal ventral gray column cells of the caudal part of the cervical portion of the spinal cord of a rhesus monkey. The nuclei are centrally located. The black spot within the nucleus is the nucleolus. The chromophilic Nissl bodies are uniformly distributed throughout the cytoplasm (10 × ocular, 4 mm. objective).

Fig. 2.—Four ventral gray column cells of the same histologic section as those shown in figure 1. The radial (musculospiral) nerve had been cut in the axillary fossa, and the monkey was killed on the eighth day after operation. Two of the cells show definite chromatolysis. In the cell at the extreme left of the figure the finely granular Nissl substance has accumulated at the periphery and toward one pole of the cell body. The nucleus is decidedly eccentric, its periphery being indefinite in the photograph, but the nucleolus is distinctly visible. In the cell toward the right lower corner of the figure the finely granular Nissl substance has gathered around the periphery of the cell body, leaving a similar clear central area. The nuclei of this and of the other two cells are not present in the section from which the photomicrograph was made, but are present within these cells in adjacent serial section. This figure illustrates the type of chromatolytic changes in the cells which one frequently encounters in descriptions of chromatolysis of somatic motor neurons. Comparison of the size of these cells with that of the normal controls shows no appreciable change in size, the magnification being the same as in figure 1 (10 × ocular, 4 mm. objective).



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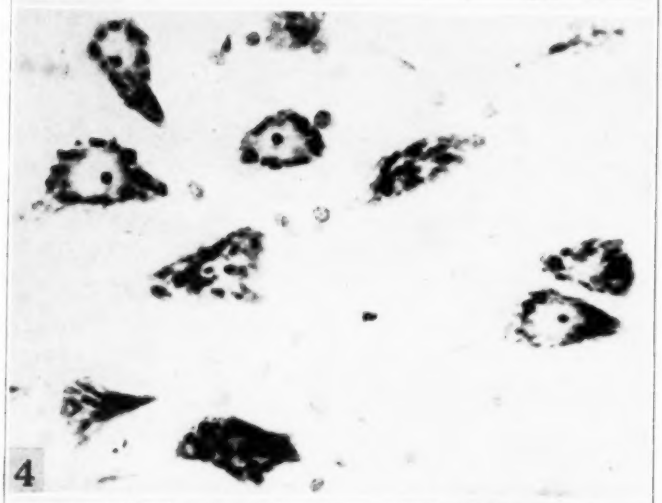

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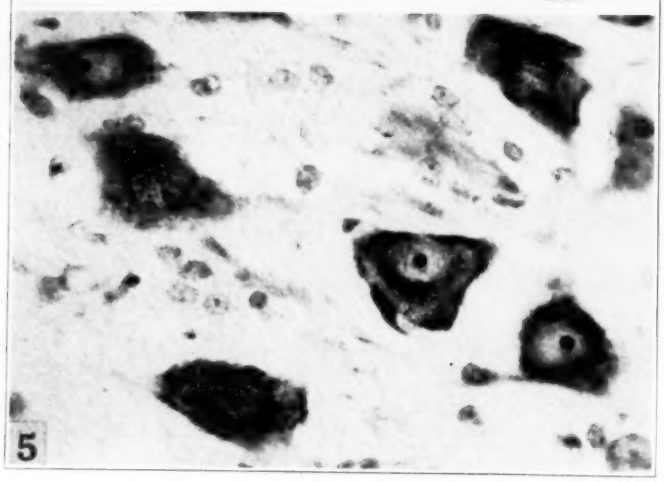

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Fig. 3.—Two cells from the ventral gray column of a rhesus monkey in which the median nerve had been cut in the axillary fossa eight days previously. The cell to the left is chromatolytic; the one to the right is normal. The appearance of the abnormal cell differs from that pictured in figure 2 in that the dustlike chromatin particles are less concentrated around the periphery of the cell and around the nucleus, and are scattered sparsely throughout the cytoplasm. The nucleus is eccentric, and the cell, because of its extreme size, has apparently undergone swelling. Figures 1, 2 and 3 were made from paraffin sections cut at 10 microns (10 × ocular, 4 mm. objective).

Fig. 4.—Normal somatic motor cells of the left hypoglossal nucleus of a rabbit. The nuclei are centrally located and the large, flakelike Nissl bodies are uniformly distributed throughout the cytoplasm (10 × ocular, 4 mm. objective).

Fig. 5.—A group of chromatolytic cells of the right hypoglossal nucleus in the same histologic section as that shown in figure 4. The right hypoglossal nerve had been divided nine days previously. The nuclei of these cells are centrally located. The Nissl bodies have undergone fragmentation and, in general, have become scattered throughout the cytoplasm. One of the cells shows them to be considerably aggregated at the periphery of the cell body and around the nucleus, leaving a lighter area between. The cells are definitely larger than the controls. Figures 4 and 5 were made from celloidin sections cut at 15 microns (10 × ocular, 4 mm. objective).

The histoologic picture of the cells of the hypoglossal nucleus, which is somatic motor, and of the dorsal motor nucleus of the vagus, which is visceral motor, of the rabbit following section of these nerves is dependent on the interval of time that elapses between the operation on the nerve and the staining of the sections. Figure 5 illustrates the appearance of the cells of the hypoglossal nucleus nine days after operation. Figure 9 shows the appearance of the cells twenty-four days after operation. Figure 11 illustrates the appearance of the cells of the dorsal motor nucleus of the vagus twenty-four days after section of the nerve.

Alterations Depending on Histologic and Functional Type of Neuron.—Relative to the changes in the cell bodies of the afferent neurons of dorsal root ganglia, Fleming [6] concluded as follows:

> The cells of the ganglia on the posterior nerve roots undergo definite changes as the result of nerve section or ligature, and do so at a much earlier period than the multipolar cells in the cord—beginning probably as early as the fourth day, and certainly by the seventh day. My results show that, up to a certain date after section or ligature, the ganglia will suffer most organic changes, but that after three weeks the multipolar cells rapidly undergo alteration, and that in six to seven weeks, according to Marinesco, Golgi, and others, disintegration of protoplasm occurs. My results, however, only show distinct disintegration of protoplasm of the cells of the posterior nerve root ganglia after fifteen to twenty weeks, although it is well marked in multipolar cells in three to seven weeks.

Fleming experimented on rabbits and dogs. Windle,[7] in a recent publication, illustrated in an excellent photomicrograph the alterations of the cells of the first cervical spinal ganglion of a cat eight days after section of the spinal accessory nerve.

The cells of the hypoglossal nucleus and of the dorsal motor nucleus of the vagus in the rabbit respond in a very different manner after section of the corresponding nerves at approximately the same distance from the brain. Figure 12 is a low power photomicrograph showing the abnormal nuclei, and figure 13 one showing the normal nuclei, in the same histologic section, twelve days after section of the nerves. Figures 15 and 17 are high power photomicrographs showing the details of changes in some of the cells of the nuclei.

All of the figures are unretouched photomicrographs of the cells of the stained sections. In each case, when chromatolytic cells are shown, the accompanying control cells are contained within the same histologic section and therefore are handled and treated in identically the same manner, thus eliminating the probable criticism that appear-

6. Fleming, R. A.: Notes on Two Cases of Peripheral Neuritis, with Comparative Results of Experimental Nerve Degeneration and Changes in Nerve Cells, Brain **20**:56, 1897.

7. Windle, W. F.: The Sensory Components of the Spinal Accessory Nerve, J. Comp. Neurol. **53**:115 (Aug.) 1931.

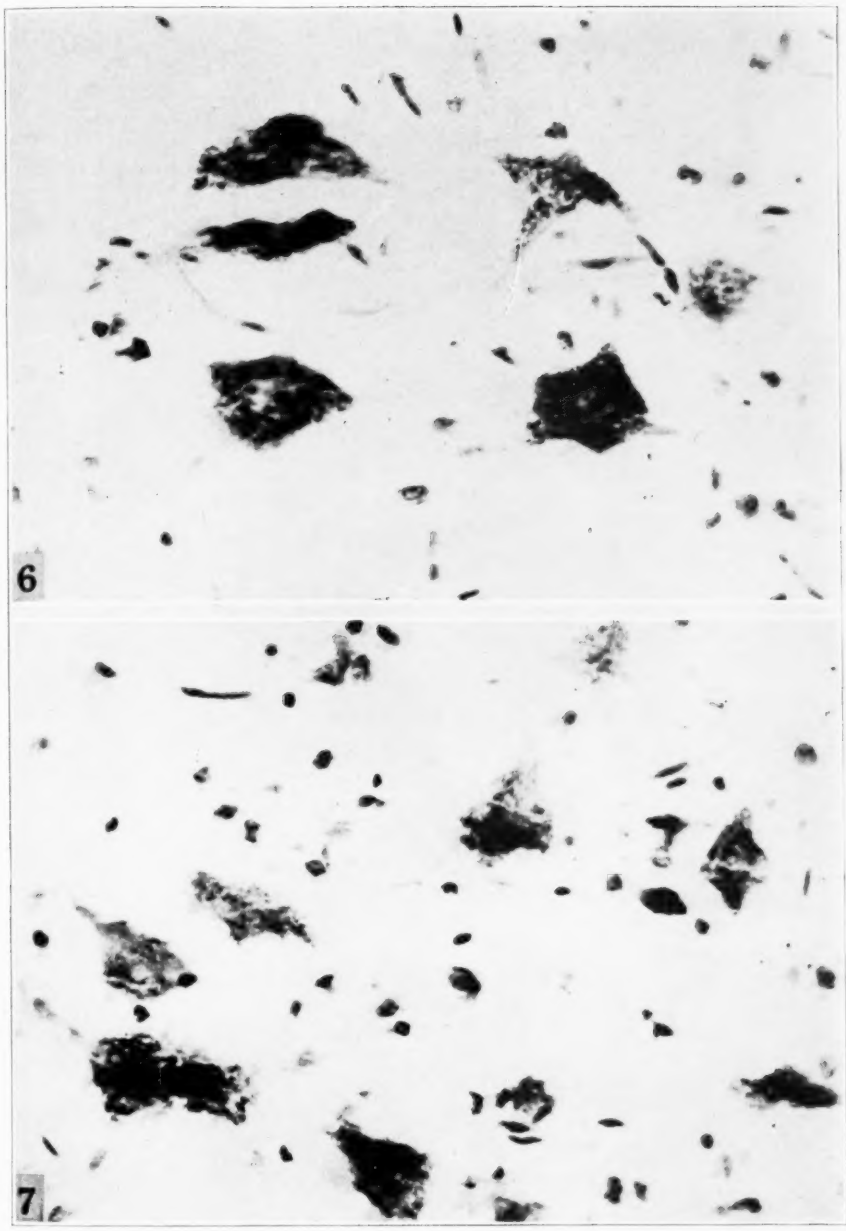


Fig. 6.—Normal somatic motor cells of the right oculomotor nucleus of a rabbit (10 × ocular, 4 mm. objective).

Fig. 7.—Chromatolytic cells of the left oculomotor nucleus of the same rabbit eight days after evulsion of the left oculomotor nerve. Many of the cells are smaller, with their outlines ragged, but still contain a moderate amount of Nissl substance. Compare the appearance of these cells with those shown in figure 2 (10 × ocular, 4 mm. objective).

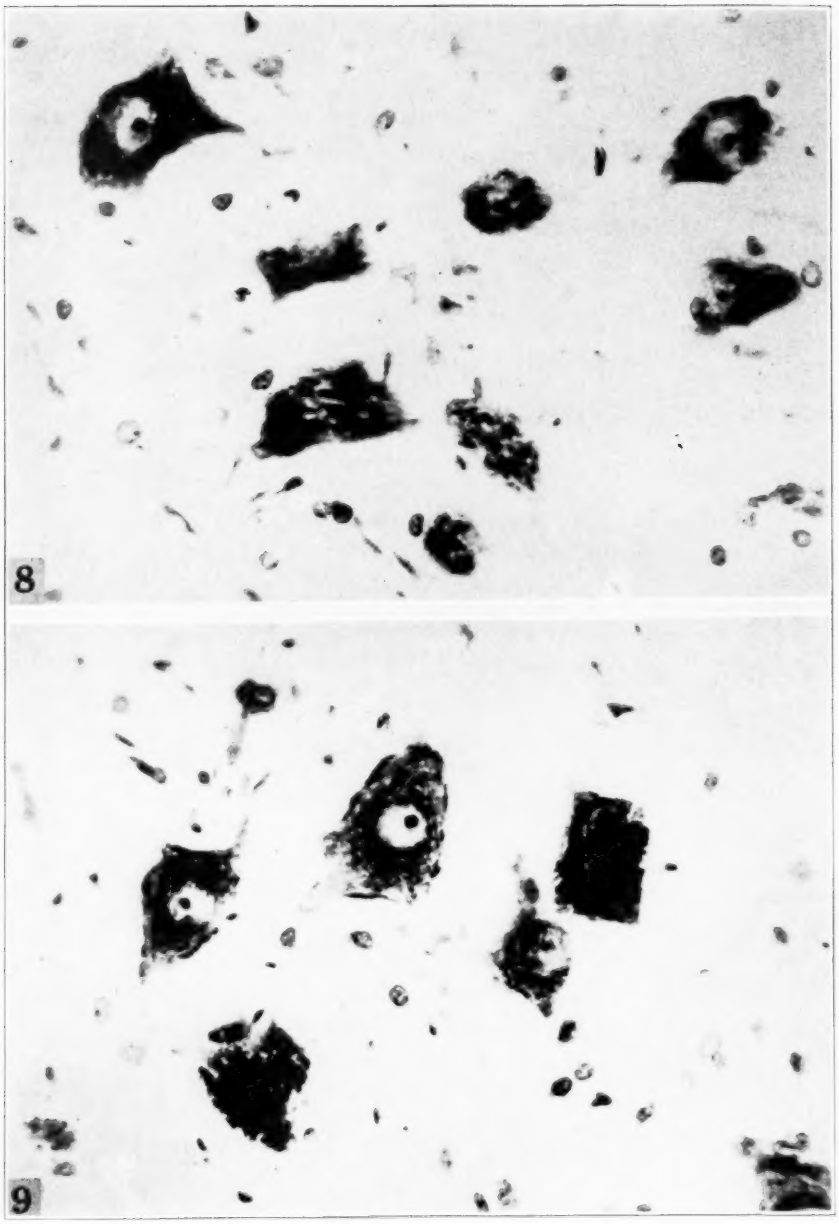
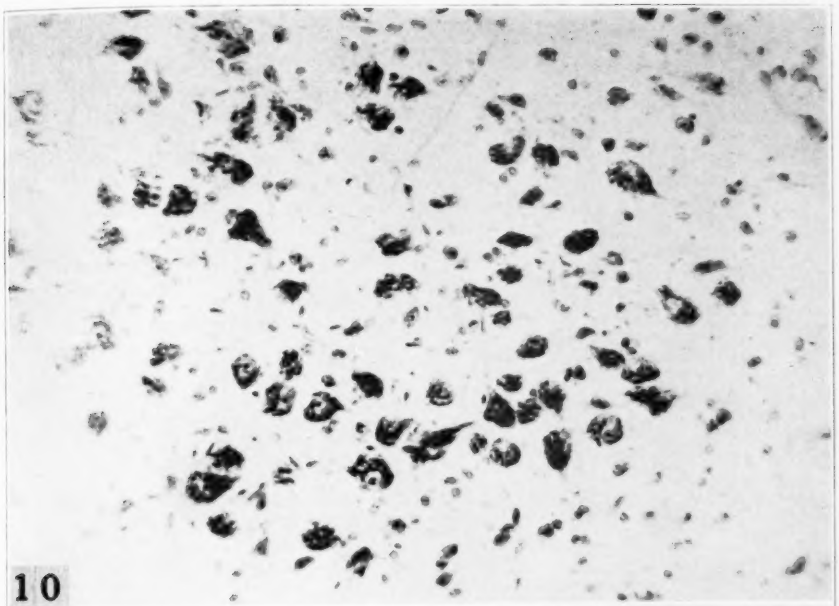


Fig. 8.—Normal cells of the left hypoglossal nucleus of a rabbit (10 × ocular, 4 mm. objective).

Fig. 9.—Recuperating cells of the right hypoglossal nucleus of a rabbit twenty-four days after section of the right hypoglossal nerve. The cells are again normal in appearance, showing distinct, large Nissl granules uniformly distributed throughout the cytoplasm. Compare with figures 5 and 15 (10 × ocular, 4 mm. objective).



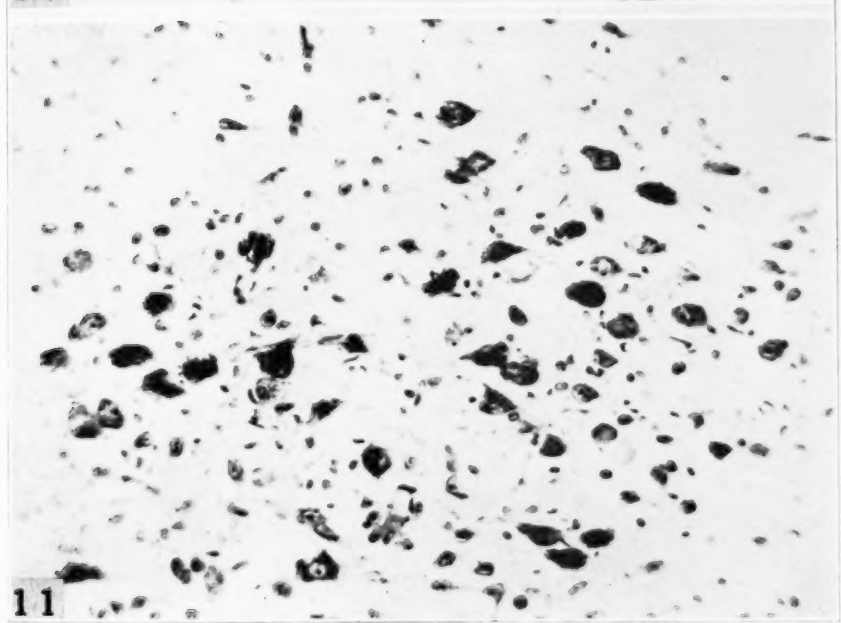


Fig. 10.—Normal visceral motor cells of the left dorsal motor nucleus of the vagus nerve of a rabbit (10 × ocular, 8 mm. objective).

Fig. 11.—Recuperating cells of the right dorsal motor nucleus of the same rabbit twenty-four days after cutting the right vagus nerve in the neck. Compare with figures 12 and 17. Figures 6 to 11 inclusive are from paraffin sections cut at 10 microns (10 × ocular, 8 mm. objective).

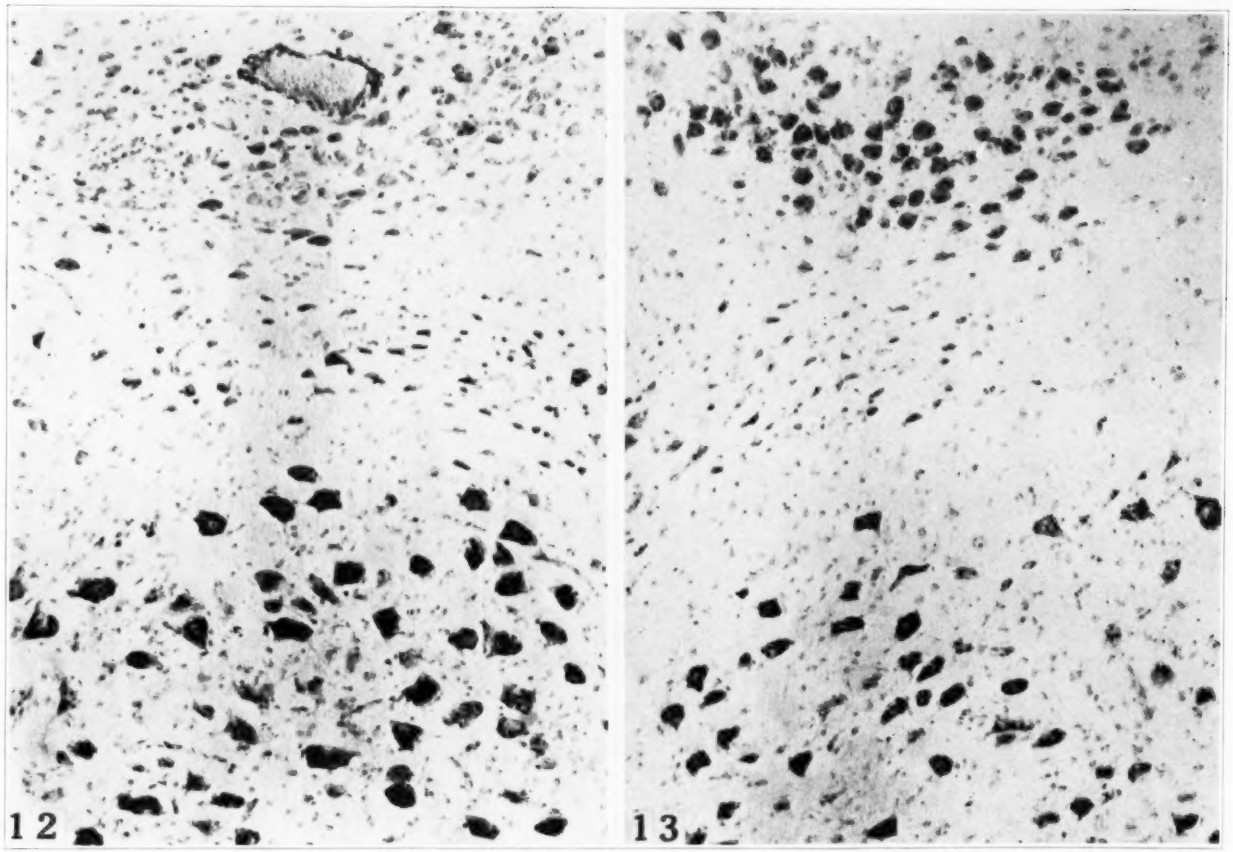


Fig. 12.—Chromatolytic cells of the right dorsal motor nucleus of the vagus nerve and of the right hypoglossal nucleus of a rabbit twelve days after section of the corresponding nerves in the neck. In the upper part of the photograph are seen the "ghosts" of the visceral motor cells of the dorsal motor nucleus of the vagus. The dark ring is a blood vessel. In the lower part of the figure are the chromatolytic cells of the somatic motor hypoglossal nucleus (10 × ocular, 16 mm. objective).

Fig. 13.—Corresponding control nuclei from the left side of the same histologic section. Compare the normal with the abnormal nuclei. In the case of the visceral motor nucleus the cells shrink, lose a considerable part of their Nissl substance and practically disappear from view when compared with the cells of the normal nucleus. The somatic motor

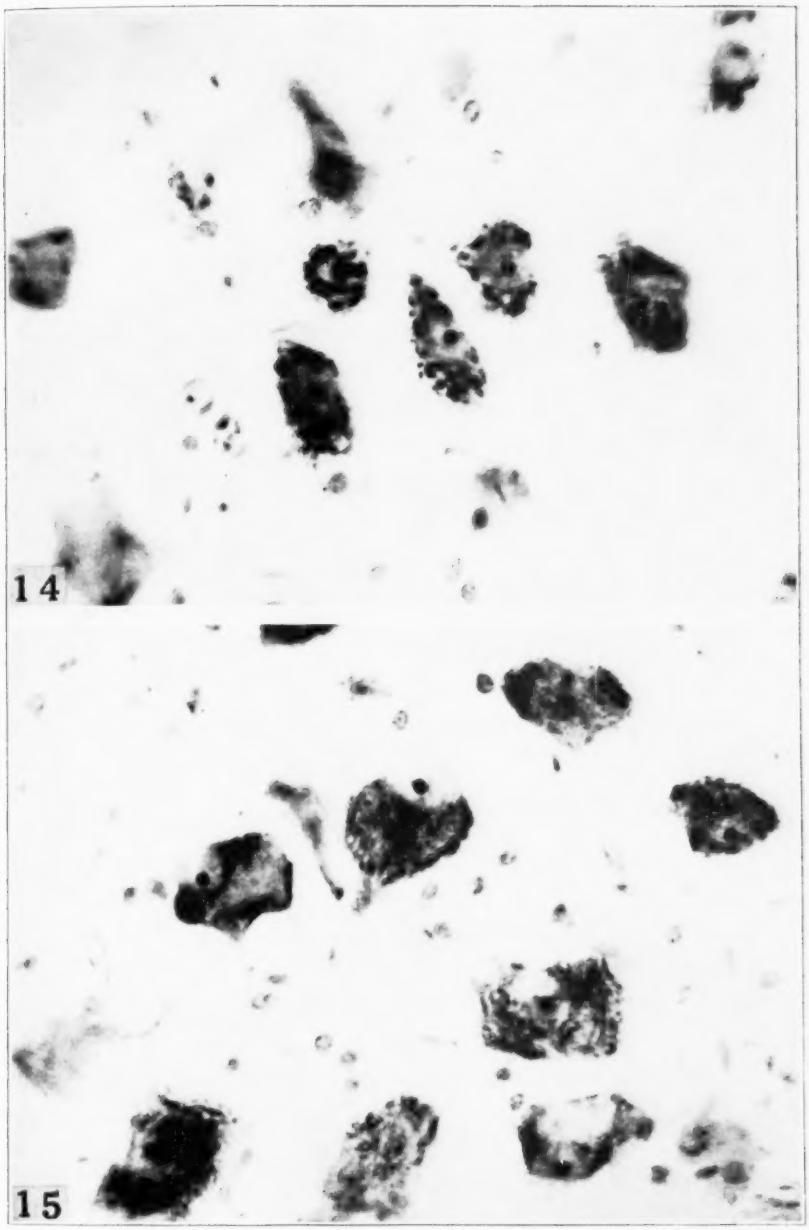
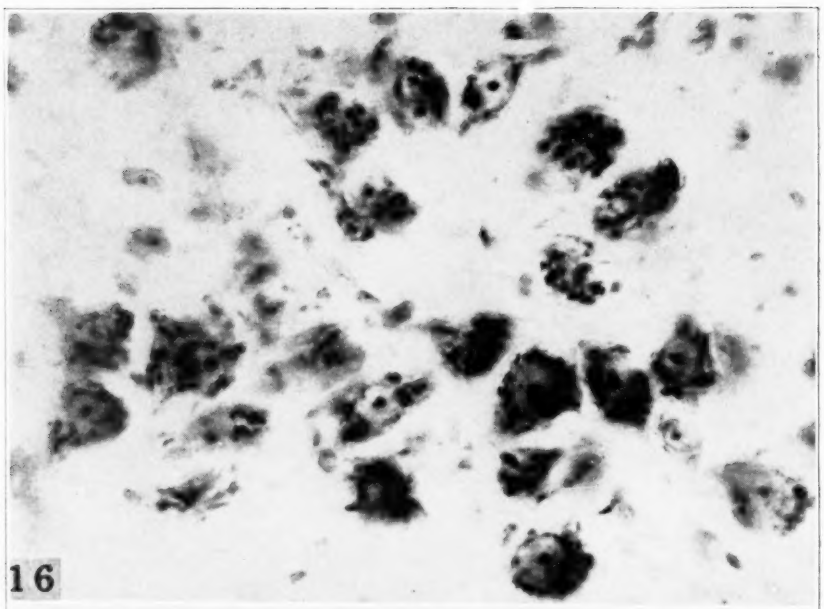


Fig. 14.—Normal hypoglossal cells of the left hypoglossal nucleus shown in figure 13 (10 × ocular, 4 mm. objective).

Fig. 15.—Chromatolytic cells of the right hypoglossal nucleus shown in figure 12. Note the finely granular Nissl substance and its disposition in the cells. Two of the cells show marked eccentricity of nuclei, even to the extent of causing bulging of the cell wall (10 × ocular, 4 mm. objective).



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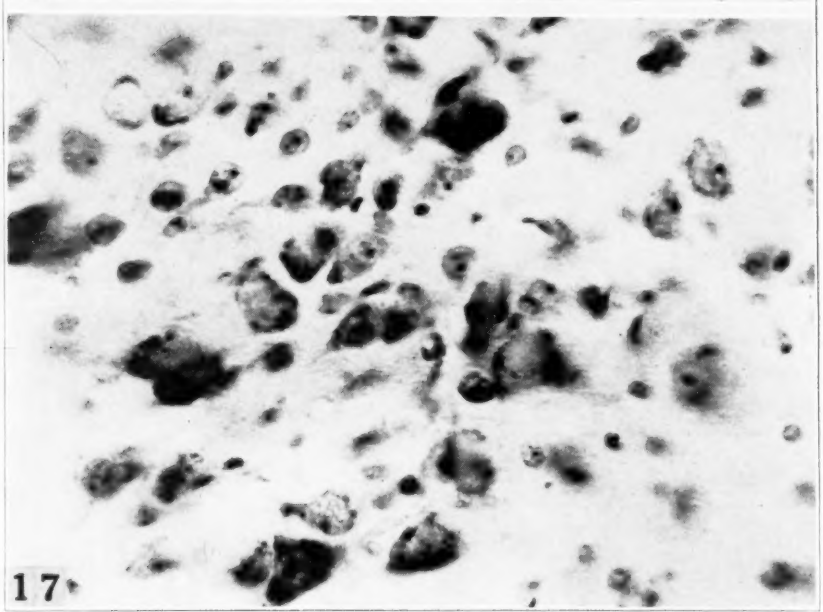

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Fig. 16.—Normal cells of the left dorsal motor nucleus of the vagus nerve shown in figure 13 (10 × ocular, 4 mm. objective).

Fig. 17.—Chromatolytic cells of the right dorsal motor nucleus of the vagus shown in figure 12. Some of the cells contain a fair amount of chromatin; others are depleted. Figures 12 to 17 inclusive are from celloidin sections cut at 15 microns (10 × ocular, 4 mm. objective).

ances may be explained on the basis of differences in fixation and staining, or as artefacts.

SUMMARY

The appearances of nerve cell bodies subsequent to section of certain peripheral nerves in the rabbit and in the rhesus monkey are extremely variable, and are expressed as chromatolysis, signifying primarily a fragmentation of the typical Nissl bodies. These granules may or may not undergo a rearrangement within the cell or in large part disappear. The cells may enlarge, shrink or fail to undergo any appreciable alteration in size. The nucleus may or may not become eccentric.

Chromatolytic changes in the cells and the reaction of the cells in general are dependent on at least four factors: (1) the type and the age of the animal used; (2) the distance from the central nervous system at which the nerve is injured; (3) the interval that elapses between the time of operation and that of histologic preparation of the material, and (4) the histologic and functional type of neuron. The appearances of efferent neurocytes exemplifying these factors are illustrated in the accompanying unretouched photomicrographs.

STATUS MARMORATUS

ETIOLOGY AND MANNER OF DEVELOPMENT

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AND
WILLIAM MALAMUD, M.D.
IOWA CITY

The grouping of a number of cases into a disease entity under a name which is based on some single feature may lead to misunderstandings. No matter how unbiased the originator of such descriptions may be, there is always a tendency to force into the group subsequent cases that happen to present this particular feature, with an attempt to fit all other features into a common picture. One finds this state of affairs strikingly demonstrated in the case of the syndrome described as "status marmoratus" by C. and O. Vogt.[1] Although a case showing all the characteristics of this group was reported by Anton[2] in 1896, it was really not until fifteen years later that the Vogts[1] described a number of cases, and in conjunction with Oppenheim established the clinical syndrome.

The most characteristic feature of this disease, and the one responsible for its designation, was that the myelin sheath preparations (Weigert) showed, besides the normal myelin, a quantity of irregular, darkly stained condensations, blotches and stripes interconnected to form a network in the gaps of which there were islands of a lighter hue. These networks were described as being particularly localized in the striate bodies. Under the higher magnifications these darkly stained structures were found to consist of fine, delicate myelinated fibers. The rest of the striatum was more or less destroyed and replaced by glia cells with small nuclei and a rich network of fibers. Grossly, the preparation with its alternation of dark and light areas resembled marble, thus giving rise to the name "status marmoratus." The concomitant

From the State Psychopathic Hospital, Ann Arbor, Mich., and the Iowa State Psychopathic Hospital, Iowa City.

Presented at a meeting of the Iowa branch of the Society for Experimental Biology and Medicine, Nov. 10, 1931 (Proc. Soc. Exper. Biol. & Med. **29**:276 [Dec.] 1931).

1. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:660, 1920.

2. Anton, G.: Ueber die Beteiligung der grossen basalen Gehirnganglien, Jahrb. f. Psychiat. u. Neurol. **14**:141, 1896.

clinical picture was described as showing itself either at or soon after birth. It consisted of spasticity, peculiar postures of the extrapyramidal type, athetotic movements and, frequently, paralysis. Of the less characteristic symptoms, compulsive laughing or crying, convulsions and mental defect were conspicuous.

In some of the cases the authors discovered the existence of more or less similar clinical manifestations in other members of the family. This fact, coupled with the early onset, led the authors to consider the disease a developmental anomaly. Furthermore, in all of the cases reported by the Vogts, although lesions of other types were found in different parts of the brain, the peculiar marble state was reported as found in the basal ganglia only. Because of this the authors believed that they were dealing with a system disease, a "pathoklitic" disease entity with a typical clinical syndrome.

It was not long after the original publication by the Vogts [1] that other observers reported cases which raised the question as to the specificity of the syndrome. Thus, for instance, Bielschowsky [3] reported a case in which status marmoratus was found in the cerebral cortex, showing that the condition was not restricted to the striate body. Furthermore, a number of investigators studying cases that undoubtedly showed the pathologic picture of status marmoratus found that neither the clinical history nor the pathologic picture was in keeping with the idea that the disease was a developmental anomaly. Anton's original case, as well as cases reported by Meyer,[4] Scholz [5] and others, indicated definitely that the lesions resulted from some acquired process, inflammatory or vascular.

Four new cases are here reported. The first three were studied both clinically and anatomically. In all of these the anatomic picture was such that no doubt can exist as to their belonging properly to the syndrome described by Vogt. Unfortunately, circumstances were such that the clinical observations were not complete. In the fourth patient, who is living, the clinical picture seems to fit so well into the syndrome that even without autopsy it can be regarded as status marmoratus.

REPORT OF CASES

CASE 1.—*A child, with a normal family history but a prenatal history of a possible rupture of the membranes two months before birth, was born at term, dehydrated and undersized. Following convulsions a few days after delivery, there*

3. Bielschowsky, M.: Ueber den Status marmoratus des Striatum, J. f. Psychol. u. Neurol. **31**:125, 1924.

4. Meyer, A.: Zur Auffassung des Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:529, 1926.

5. Scholz, W.: Zur Kenntnis des Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:355, 1924.

were spasticity of all the limbs, bilateral squint and nystagmus. Thereafter followed a gradually increasing retardation of both physical and mental development and death at 26 months. Autopsy revealed a small brain with atrophic and microgyric convolutions and reduced white matter. The striate body and thalamus showed even grossly the characteristic picture of a status marmoratus. The leptomeninges were thickened and infiltrated, and in the cortex there was diffuse and "layer" destruction with glial replacement. In the caudate, putamen and thalamus there was also a pronounced glial scar formation. The scars in the cortex were only slightly myelinized, whereas those in the striatum and thalamus showed the typical myelin bundles which have given rise to the name of status marmoratus. The white matter was shrunken and scarred throughout.

Clinical History.—A. J. W., a white boy, who was born on Aug. 20, 1928, was admitted to the Michigan Home and Training School on Aug. 28, 1929, with the complaint of retarded development. The family history was unimportant. The parents were normal. During the pregnancy, while the parents were in China, the mother was living under rather unsatisfactory hygienic conditions. During the seventh month of pregnancy, following an automobile ride over rough roads, the mother believes that the amniotic sac broke. At birth, which was at full term, the baby appeared dehydrated. Otherwise, the child showed no abnormal features.

On the second day after birth, the child is said to have had a "cerebral hemorrhage," with convulsions which continued for seven days. Following this it was noticed that the limbs were spastic. The general health following this was fair. In May, 1929, a physical examination showed the following features: bilateral squint; some suggestion of a microcephalic head, with both fontanels closed, and some spasticity of all extremities. There were a lateral nystagmus and congenital cataracts in both eyes. The neurologist considered the case to be one of infantile cerebral hemorrhage and mental deficiency.

A month after admission to the Michigan Home, a mental examination was attempted, and an approximate mental age of 3 months was estimated. "The baby lay in bed like a young infant, made almost no response to social stimuli, did not react to sudden sounds, and binocular coordination was doubtful. He would carry an object to his mouth, blink at something threatening his eyes, and hold an object in his hand for a short time."

The course at the home showed nothing noteworthy other than a gradual decline and death on Oct. 9, 1930.

Postmortem Examination.—Gross Pathology: The brain was small, weighing 613 Gm. (right hemisphere, 235 Gm.; left, 243 Gm.); the cerebellum, pons and medulla weighed 135 Gm. The convolutions showed pronounced atrophy and microgyria in the region of the occipital lobes and the median surface. The leptomeninges were somewhat thickened; the basal vessels were delicate. Sections through the frontal lobe showed a pronounced decrease of white matter, some convolutions being practically devoid of it. There was also a marked reduction of white matter in the parietal and occipital lobes, especially in the region of the microgyria. Both lateral ventricles were enlarged. The basal ganglia were well outlined. The caudate nuclei were reduced in size and traversed by small white foci and lines. Similar foci were seen in the putamen and thalamus.

Histologic Examination: The meninges were markedly thickened, with diffuse lymphocytic infiltrations and occasional lymphocytes in the adventitia of the vessels, which were otherwise not changed.

The cortex: The changes were present in almost all regions, and consisted of a destruction of the parenchyma and its replacement by glial scars. In the areas grossly characterized by microgyria the destruction seemed to involve certain

layers in preference to others. This varied from total destruction of all the layers but one to an involvement of isolated layers, with the others either intact or only slightly involved. In the latter areas, one could actually see instances of so-called layer degeneration in which apparently the third layer seemed to have suffered most frequently. In the calcarine area the fourth and the sixth layers were destroyed (fig. 1). In some parts of the frontal and temporal regions and in both cornua ammonis, the cortex was practically intact.

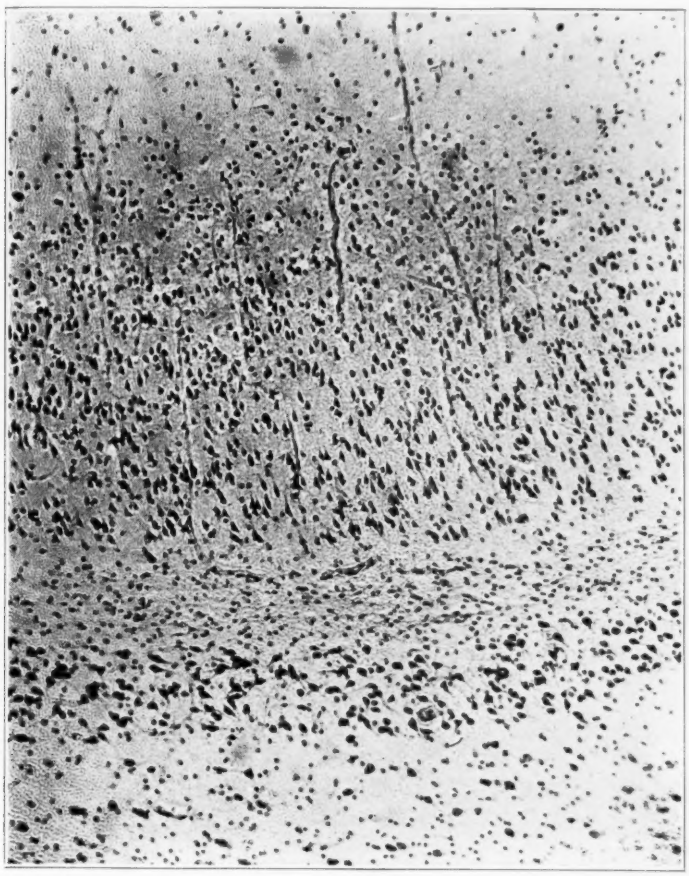

Fig. 1.—Severe layer disturbance of the fourth and sixth layers in the occipital lobe. Nissl stain; × 40.

The Holzer stain revealed extensive glial scars which had developed on the ruins of the parenchyma. These were proportional in degree to the loss of the architecture. In those regions where small solitary cortical sectors had been destroyed, the islands of glial scars replacing them spread out diffusely in the cortex and formed pictures that resembled closely the so-called "plaques fibro-myéliniques" (fig. 2). These faded off, on the one hand, into isolated glial islands, and, on the other, passed over into large areas of complete scar formation. The Holzer pictures showed particularly well the regions in which layer destruction

had taken place, as in such places the glial scar took the form of a narrow, layer-like arrangement between adjacent intact layers of parenchyma (fig. 3).

The condition of the axis cylinders followed closely that of the cyto-architectonic, being fairly well preserved where the latter was least affected and markedly reduced especially in the regions of the layer degeneration.

The myelo-architectonic, however, seemed to have been affected more severely and practically everywhere in the cortex, so that even in those regions where both cells and axis cylinders had been fairly well preserved the myelin had suffered out of proportion. In keeping with this and contrasting with the findings in the basal ganglia, myelinization of the cortex was practically absent. Only in a few

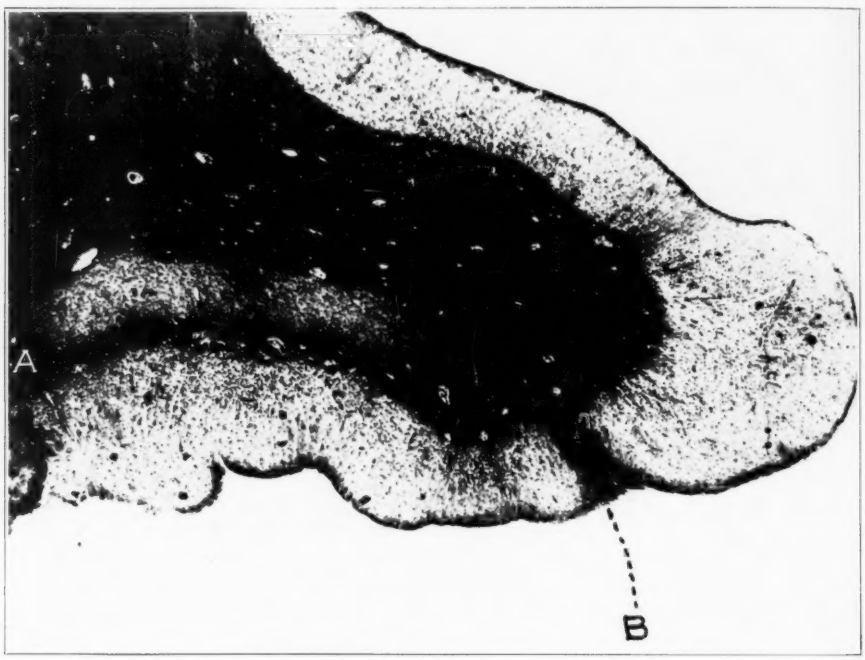

Fig. 2.—Severe scar formation of the cortex. *A* shows a layer-like scar; *B* shows a plaque fibromyélinique. Holzer stain; × 10.

isolated scars could one find single myelin fibers of the newly formed type, and they never occurred in the form of bundles.

The basal ganglia: The caudate showed pronounced parenchymatous destruction with replacement by glial scars, containing numerous small nuclei and only isolated, markedly affected ganglion cells. Now and then one could see islands of more or less well preserved parenchyma (fig. 4). This was true of the whole nucleus, and at some points the lesion had spread into the capsule.

The same change was seen in the putamen.

In the pallidum no scars were found, and the parenchyma seemed to have suffered very little.

With the Nissl stain, the thalamus showed the same picture as was found in the striate body. The disturbances were most severe in the medial nucleus.

Fig. 3.—Severe scar formation in the cortex. Glial proliferation in the white matter. Plaque-like foci. Holzer stain; × 10.

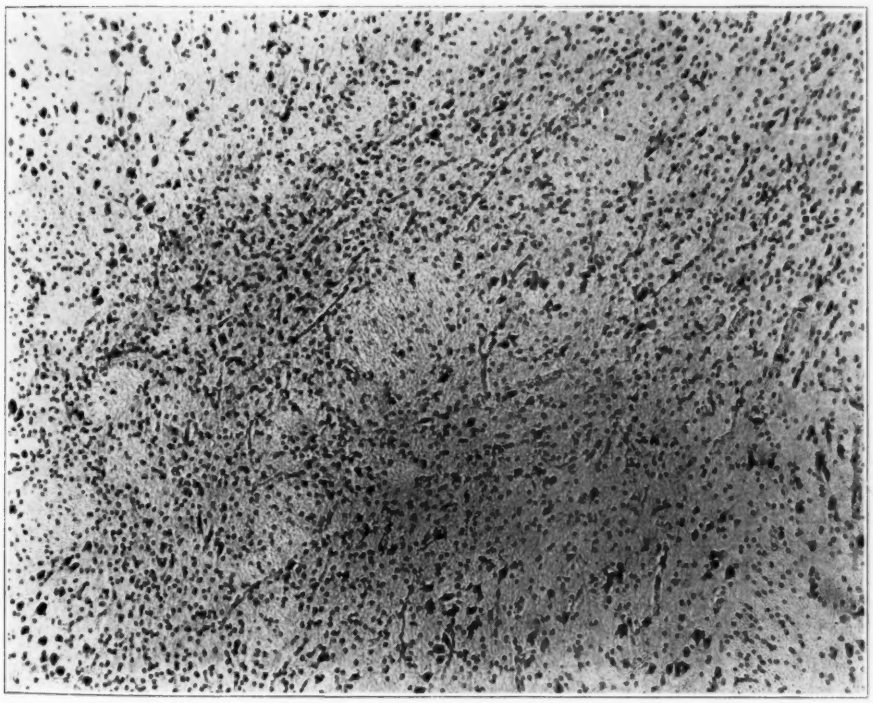

Fig. 4.—Thick glial scar in the putamen. Only a few shrunken ganglion cells are left near the scar. Nissl stain; × 40.

In the basal ganglia, the characteristic features of the status marmoratus were particularly well shown in Holzer and Weigert sections. With the Holzer stain, the caudate, putamen and thalamus all showed a diffuse glial fibrous network, the individual fibers of which were delicate. Where these fibers were arranged in thick bundles with intervening more or less free spaces, a definite marble appearance was obtained (fig. 5). The pallidum showed an altogether different picture, because here the tendency was toward an even, diffuse distribution of the fibers.

In Weigert preparations a pronounced myelinization of the scars in the caudate and putamen could be seen. Running right through the glial scars there were bundles of fine, delicate, weakly staining myelin sheaths. These characteristics

Fig. 5.—Large stellate scar in the putamen. Holzer stain; × 10.

and the peculiar manner of their arrangement definitely differentiated them from the normal (figs. 6 and 7). They seemed to exceed in quantity the axis cylinders, but they were not quite as numerous as the glial fibers.

The pallidum and thalamus differed from the striate body in that here, where normally a larger quantity of myelin occurs, there was no similarity to a marble state; the two nuclei seemed to be poorer in myelin than is normally the case.

Bielschowsky stains showed a reduced quantity of axis cylinders, especially in the regions of the scars. There was no indication of regeneration of axis cylinders, their caliber being very fine.

The subthalamic bodies, the red nuclei and the substantia nigra showed no changes. In the substantia grisea centralis there was a widespread scar formation.

The white matter throughout the brain had suffered a great deal. Even with the Nissl stain one could see numerous glial scars, which were particularly pronounced in the parietal and occipital lobes.

The Holzer stain brought out the changes most strikingly, showing a thick glial production with occasional small pores (figs. 2 and 3). There was persistence of some axis cylinders in the scars, but they varied in numbers. The glial scars contained numerous myelin sheaths, and in a number of regions the different tracts were well recognized. Thus, for instance, such structures as the corona radiata, the corpus callosum, the anterior commissure and the tapetum, although at times somewhat narrower, were nevertheless easily recognizable.

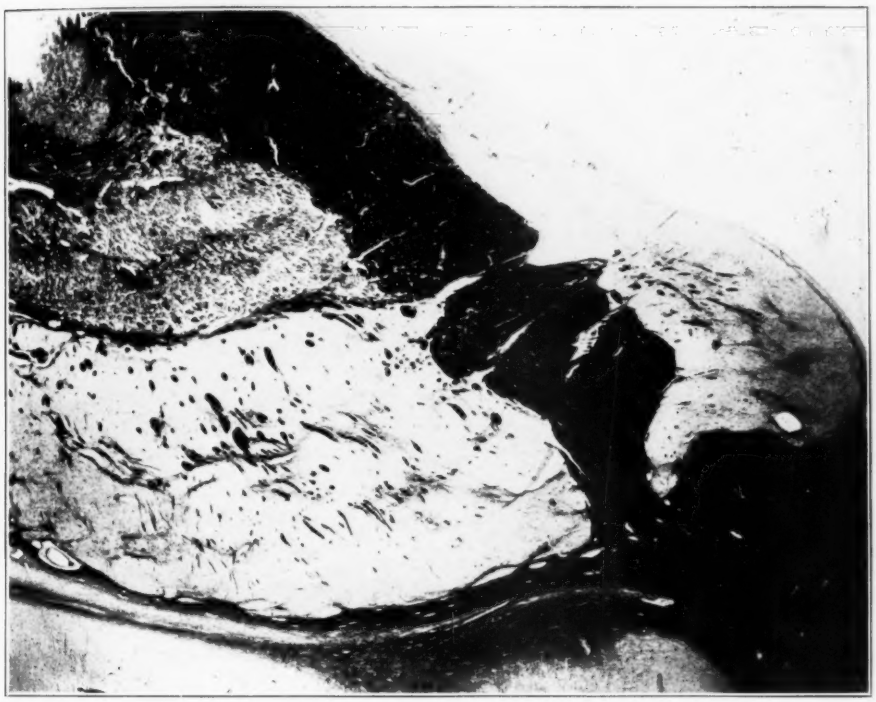

Fig. 6.—Typical status marmoratus in the caudate and putamen. The pallidum is slightly demyelinated. Weigert-Kulschitzky stain; × 10.

Cerebellum: There were a few scars in the molecular zone, but no other lesions in the cellular structure. The white matter, however, was definitely reduced.

Fat stains showed no occurrence of fat anywhere. Occasionally one found some small quantities of iron. The axis cylinders showed no degenerative or regenerative features, whereas the myelin sheaths, although irregular in caliber, were otherwise well preserved. There were no pathologic changes in the spinal cord.

CASE 2.—*An infant, aged 8 months at the time of death, whose family and prenatal history was unimportant, was born by forceps delivery, but with no apparent injury. Subsequent development was normal up to the end of the third month; then, convulsions, spasticity and interference with further mental progress occurred.*

There were premature closure of the fontanels, oxycephaly, nystagmus and some spasticity. Two operations were performed for the oxycephaly, death occurring two days after the second. Pathologically, the outstanding features were: grossly, atrophy of the cortex with several areas of microgyria, marked reduction of the white matter and scar formation in the caudate nucleus and putamen; histologically, thickened and infiltrated meninges, destruction of the parenchyma with the

Fig. 7.—Fine myelinated fibers arranged in bundles and showing how they differ in structure and staining from the normal. Weigert-Kulschitzky stain; × 40.

formation of glial scars without myelinization and occasional infiltration of the cortical vessels. In the caudate, putamen and thalamus, there were diffuse destruction of the parenchyma and the formation of glial scars with myelinization of these, producing the typical picture of status marmoratus. Diffuse glial production was present in the pallidum.

Clinical History.—S. I. H., a white, American girl, aged 7 months, was admitted to the Pediatrics Department of the University Hospital at Ann Arbor, Mich., on Jan. 21, 1931. The mother stated that the mental development was retarded.

The family and prenatal history was unimportant. Delivery was at full term, but was prolonged, and instruments were used. There were, however, no injuries, and for the first three months the child appeared normal. At the end of the third month she began to have spells, occurring about from six to twelve times a day and lasting for several seconds. During these spells the patient's head was bent down, the shoulders were raised, and the body was doubled up. The eyes rolled up, and she occasionally quivered all over the body.

On admission, an examination showed a well nourished child of the age stated. The head was held at a markedly retracted position. Both fontanels were closed, the head being somewhat bullet-shaped. There was a nystagmus, but otherwise no peculiarities were noted. Ophthalmologic examination, tests of the spinal fluid and other laboratory tests revealed nothing of importance. The neurosurgeon made a diagnosis of oxycephaly and advised linear craniectomy. Operation was performed on the right side of the head on February 7; postoperative recovery was fairly good. Another operation was performed on February 21. Two days after the operation, convulsive seizures, severe nystagmus of the eyes, retraction of the head and muscular spasms developed. The patient grew gradually worse and died on February 23.

Postmortem Examination.—Gross Pathology: The brain was asymmetric, the right hemisphere being smaller than the left. The leptomeninges were somewhat cloudy. The convolutions of the right temporal lobe were microgyric in type. There was a lesion, about 1 inch (2.5 cm.) in diameter, in the right frontoparietal region which caused some indentation of the convolutions. The convolutions of the occipital lobe, as well as of the left hemisphere, appeared to be generally better preserved. On the median surface of both hemispheres there was a yellowish lesion occupying practically all of the frontal and parietal lobes. The convolutions of both sides of this region were atrophic. On section, the gray matter was indistinct and narrow; the white matter was hard in consistency and greatly reduced. The basal ganglia were indistinctly outlined. The caudate nucleus, putamen and thalamus showed advanced scar formation.

The pons, cerebellum and medulla appeared to be normal.

Histologic Examination: The meninges were definitely thickened, and in numerous places showed lymphocytic and plasma cell infiltrations, both in the tissue and in the adventitia of the vessels (fig. 8).

Cortex: In Nissl preparations one could see, even under low magnification, that the whole cortex was studded with numerous foci of varying size and shape, very few areas retaining the normal structure. Higher magnifications revealed these foci as practically devoid of ganglion cells and consisting of glial tissue (fig. 8). There were slight lymphocytic infiltrations in the adventitia of some of the smaller cortical vessels.

The glial scars were particularly well brought out by the Holzer stain; they consisted of glia fibers, frequently identical with "plaques fibromyéliniques" (fig. 9).

Bielschowsky sections showed the presence of a few isolated axis cylinders, the cortex being altogether devoid of them in some places.

The myelo-architectonic was severely affected, most areas showing only isolated fine myelin sheaths without the normal arrangement. They stained poorly and had numerous regeneration bulbs. In the scars no signs of myelinization were found. This change was equally severe in both hemispheres, the parietal and temporal lobes as well as the islands being particularly severely affected.

The basal ganglia: The caudate nucleus was penetrated by numerous glial scars and glial islands, consisting of cells with relatively large round nuclei. In the regions of these scars the parenchyma was destroyed and only isolated ganglion cells could be seen. The whole nucleus was affected.

The putamen showed a similar condition.

The pallidum presented a relatively well preserved parenchyma and contained no scars.

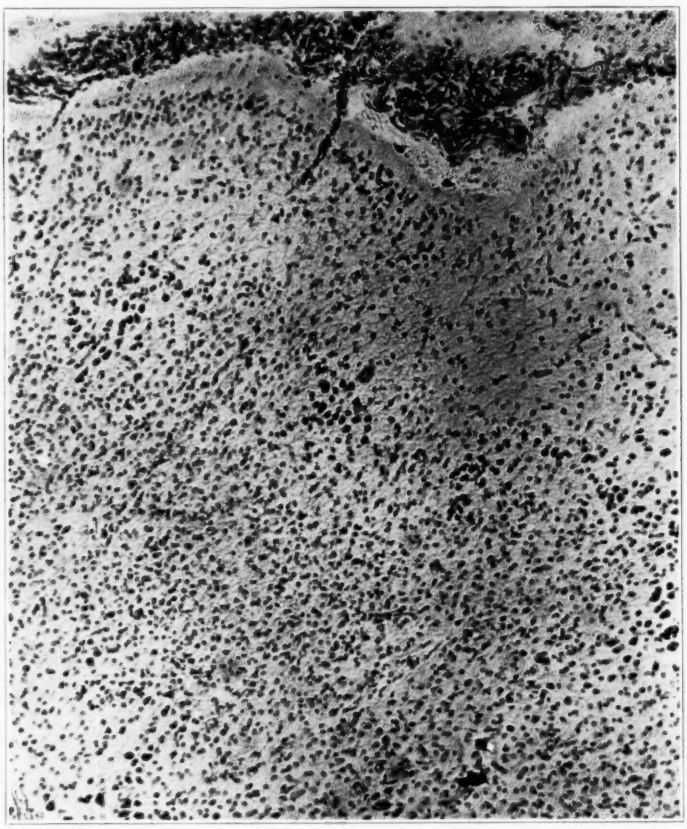

Fig. 8.—Chronic meningitis. Severe destruction with scar formation in the cortex. Nissl stain; × 40.

The thalamus showed a severe destruction of the parenchyma of a rather peculiar type, with calcification of the ganglion cells, which stained a violet red. These cells were embedded in glial scar tissue. Bielschowsky preparations revealed a large quantity of fine axis cylinders arranged in bundles and without signs of regeneration. Holzer sections yielded, in the caudate, putamen and thalamus, a picture characteristic of the status marmoratus. But whereas the first two showed the classic picture (fig. 10), the thalamus was so thickly scarified in the center that only the periphery showed the marble-like state. The glial network was increased in the pallidum but was diffuse in type.

Fig. 9.—Pronounced scar formation in both the cortex and the white matter, resembling plaques fibromyéliniques. Holzer stain; × 10.

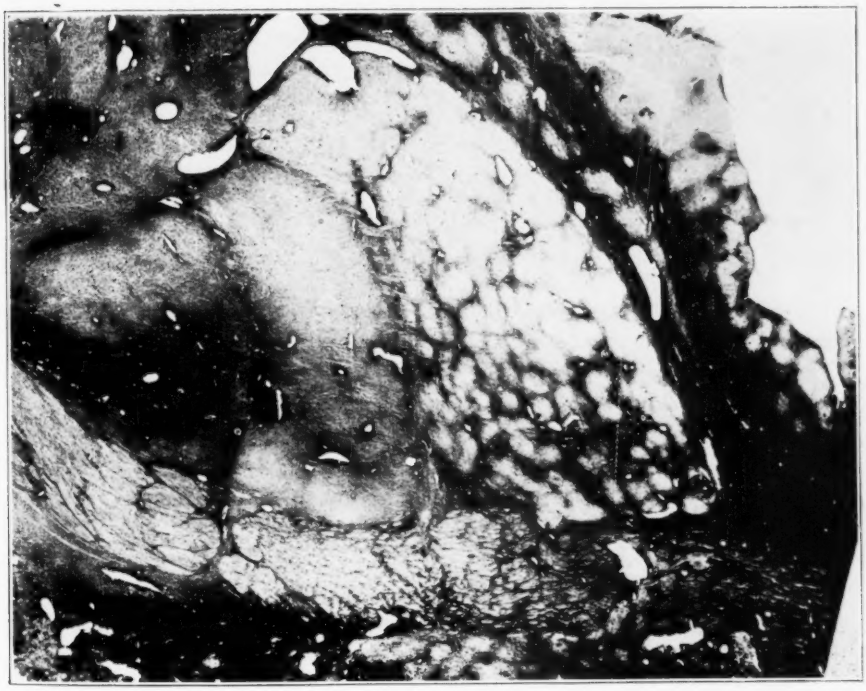

Fig. 10.—Typical status marmoratus in the putamen and cortex. Diffuse glial fiber network in the pallidum. Severe scar formation of the white matter. Holzer stain; × 10.

Weigert sections disclosed a fine myelin network in the scars of the putamen. The myelin sheaths arranged in bundles were of a fine and delicate texture and spread in all directions (fig. 11).

The myelin was decreased in the pallidum and thalamus, but no status marmoratus was present.

The subthalamic bodies, the red nuclei, the substantia nigra, the pons and the medulla contained numerous glial scars, but the cerebellum was free from pathologic changes.

The white matter of the hemispheres contained numerous glial scars throughout. These were diffuse in some places and formed islands in others. Axis cylin-

Fig. 11.—Newly formed myelin fibers arranged in bundles in the putamen. Weigert-Kulschitzky stain; × 40.

ders were few, some of them being calcified. Myelinization of the white matter was greatly retarded, the pyramidal tracts being the only myelinated unit.

CASE 3.—*Birth was uneventful, but the child had to be resuscitated. No significant features were noticed until the age of 5 years, when, following a two months' illness, the child began to show mental and physical deterioration. Six months later, she was admitted to the Michigan Home and Training School, an imbecile, unable to stand or walk, and with spasticity of the legs. There was a gradual decline, and death due to a pulmonary abscess occurred at the age of 13. Postmortem examination showed a small brain with microgyria and reduction of both white and gray matter. Histologically, the meninges were thickened; in the cortex there was a diffuse, widespread pathologic change in the vascular system,*

around which there were glial scars traversed by unusually arranged bundles of myelin sheaths. The picture was that of status marmoratus of the cortex, developed around the thickened blood vessels. The basal ganglia were practically intact.

Clinical History.—A Negro girl was born on Aug. 15, 1917, by a normal delivery, but the child had to be resuscitated. The family and prenatal history was unimportant. There were no diseases in infancy. At the age of 4½ years there was a two months' illness, starting with a "sore mouth," following which the child failed to recover completely; she was admitted to the Michigan Home and Training School on Nov. 24, 1922.

On admission, the examiner noted: "Child absolutely unable to do anything for herself; cannot stand or walk; legs are spastic; she drools saliva; is unable

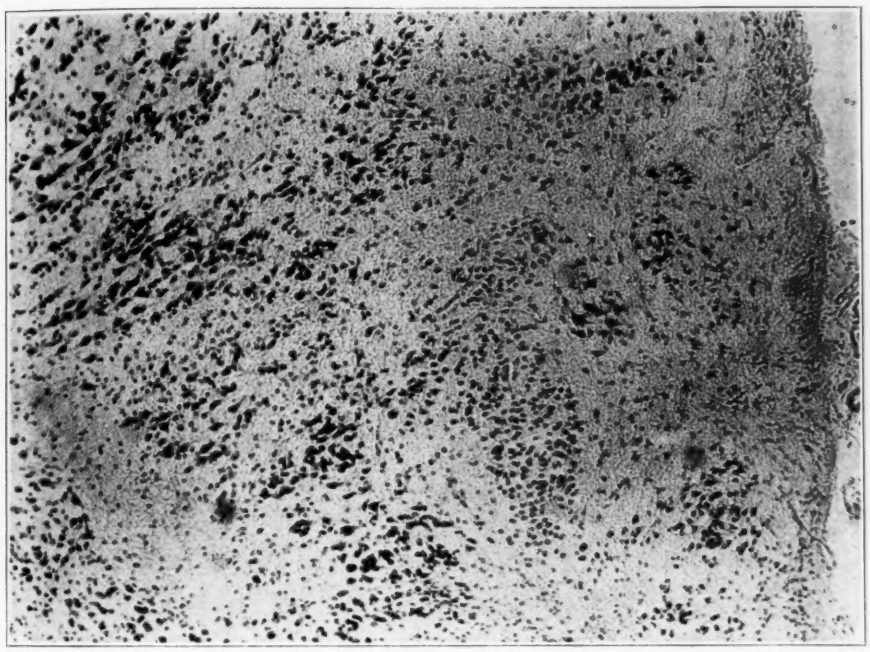

Fig. 12.—Numerous foci in the cortex in all layers. Nissl stain; × 40.

to talk. She is humpbacked and somewhat microcephalic." A mental examination showed her to be at the imbecile level; later, she dropped to the level of idiocy. She took no interest in her environment. She just sat in a chair, swaying back and forth, or crept around on the floor. She did not talk, but emitted "many noises," and was extremely untidy. In the fall of 1930 she had an inflamed throat; an abscess of the lung developed, and she died on October 23.

Postmortem Examination.—Gross Pathology: The brain was small, weighing 718 Gm. (right hemisphere, 280 Gm.; left, 279 Gm.). The hemispheres did not cover the cerebellum. The leptomeninges were thin and smooth. There was some atrophy of the convolutions of the frontal, temporal and parietal lobes. Areas of microgyria were present in the occipital lobes, especially on the right side.

In frontal sections the gray matter was narrower than normal, and was atrophic in the region of the microgyria. The white matter was greatly reduced through-

out the brain, and there was a small pore in the region of the right calcarine area. The ventricles were enlarged. No gross pathologic change was found in the cerebellum, pons or medulla.

Histologic Examination: The meninges were thickened, but did not show any signs of recent inflammation.

Cortex: The Nissl stain showed the presence of pronounced disturbances, both a diffuse loss of cells and glial foci of varying sizes (fig. 12).

The cortical vascular system showed a striking picture, which was present throughout the cortex. There were proliferation and thickening of the walls of the vessels and a pronounced increase of glial nuclei around the vessels.

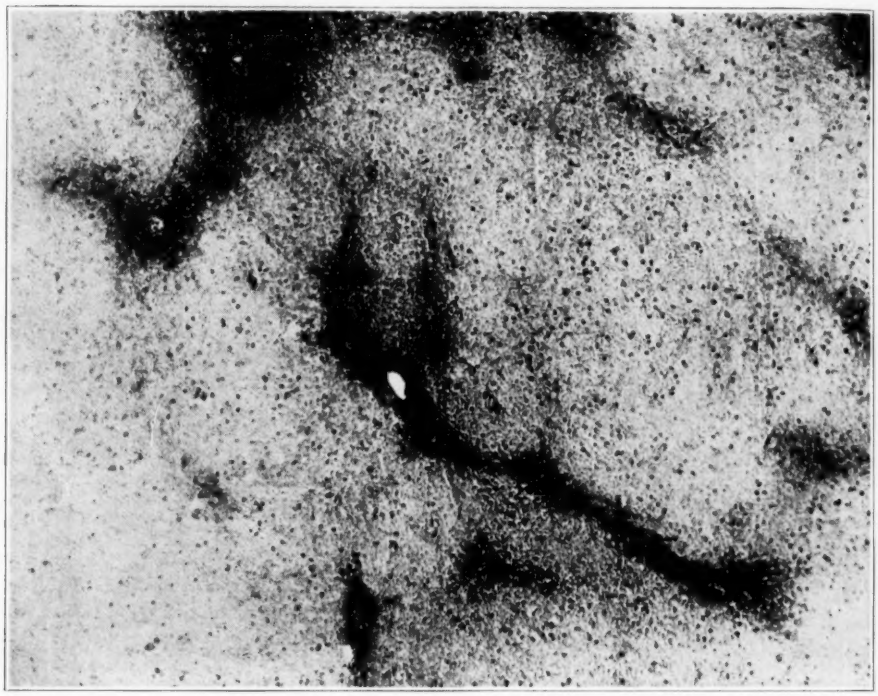

Fig. 13.—Thick glial scars arranged around the blood vessels. Holzer stain; × 10.

The Holzer stain demonstrated the glial nature of the scars, and showed definitely the arrangement of the glia fiber bundles around the blood vessels. So much so, that in this preparation one gained a picture of the whole vascular system caught in a network of glial striae (fig. 13). Axis cylinders were greatly reduced in the affected areas.

In the Weigert preparations one could see a widespread myelinization of the cortical scars around the vessels. The pictures obtained by this method were much like the Holzer specimens in that here the fibers (in this case myelin) were arranged in the form of a network of thick bundles around the whole vascular system. This unusual localization and distribution of the myelin fibers gave a definite marble appearance (figs. 14 and 15).

Fig. 14.—Compact bundles of myelin fibers surrounding the vessels and giving the picture of a typical status marmoratus. Weigert-Kulschitzky stain; × 10.

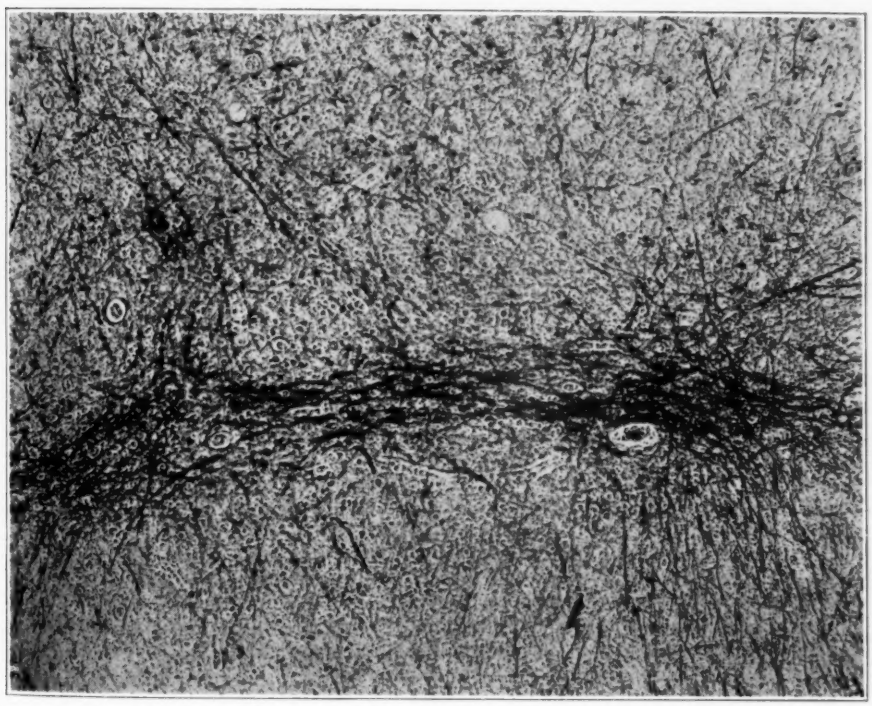

Fig. 15.—Myelinization of the glial scars around the vessels under higher magnification. Weigert-Kulschitzky stain; × 40.

As in the first two cases, the pathologic myelin fibers were thin and delicate and stained poorly.

In the white matter there were numerous glial scars, and both axis cylinders and myelin sheaths were diminished in quantity.

Basal ganglia: The putamen, pallidum and thalamus presented normal conditions, whereas in the caudate there were a few small foci of cellular loss and glial scars around some of the vessels. The vessels themselves were only slightly thickened. The Holzer and Weigert methods showed that these slight disturbances were similar in nature to those of the cortex. The pons, medulla and cerebellum were normal.

In presenting the fourth case with the previous three cases, which were definitely shown histologically to belong to this syndrome, we are aware that in the present state of our knowledge one can speak only in terms of probabilities where a diagnosis in vivo is concerned. Nevertheless, the development and clinical picture seen in this case were so much like the cases described in the literature that we felt justified in assuming that it was representative of at least a certain group of cases in which a postmortem examination showed the presence of a status marmoratus.

Case 4.—*Clinical History.*—E. Y., a white, American girl, aged 11 years, whose family and prenatal history was unimportant and whose birth and early months of development were normal, at about the age of 1 year had an attack of measles, during which she began to have convulsions which recurred every two or three months. They were described as lasting from two to fifteen minutes, with complete unconsciousness and stiffening out, then clonic movements with some frothing at the mouth, followed by a long period of sleep. The convulsions became gradually worse, and a temporary loss of the use of the left arm was noticed. Two years before admission, following a series of ten convulsions within an hour and a half, there was gradually increasing mental and physical retardation. When 19 months of age she began to walk, but because of the gradually increasing spasticity and weakness of the lower limbs, this had become progressively less adequate. The patient began to say a few words at the age of 17 months, but had not increased her vocabulary. She had never controlled her urine and feces and had never been able to dress herself, but she could feed herself. She had a tendency toward destructiveness, trying to tear and break things that came within her reach. In 1927, she was taken to the State Psychopathic Hospital in Iowa City.

Examination showed her to be undersized and undernourished, with spastic arms and legs and an awkward shuffling gait. The deep reflexes were diminished, but present. There were athetoid movements of the arms. Mentally, she was extremely distractible, could say only six or eight words and was classified as an idiot.

She was reexamined on Aug. 28, 1931. The convulsions had been occurring about two or three times a month, and consisted of twitchings followed by rigidity; they involved both sides. There had been further deterioration in that at this time she was unable to talk, dress or feed herself. She could still indicate simple needs by pointing at, or moving toward, the object desired. The gait was much impaired, with spasticity in both legs, but more in the left; the head was consistently tilted toward the left; the arms were held in a flexed position and were spastic. There was hyperextension of the hands and fingers, especially on the left side, with

athetoid movements in both hands. No choreiform movements were noted. The pupils were normal in size and reaction. There were no definite signs of involvement of the cranial nerves. All deep reflexes were increased, but equal, with a definite Babinski sign on the left and an equivocal one on the right. The abdominal reflexes were normal. The ocular fundi were normal. The examiner (Dr. T. S. Hill) thought that the diagnosis was that of a progressive mental and physical deterioration due to an organic disease of the brain, and advanced the possibility of this being a status marmoratus.

COMMENT

The clinical observations in our first three cases were of such a nature that they do not permit definite conclusions. The establishment of a parallelism between the different neurologic findings and their anatomic substratum is rendered difficult by the fact that the lesions were diffuse. The important points are:

1. None of the cases showed any relevant facts in the family history.

2. The onset of the disease, although at first glance appearing to coincide with the birth of the patient, actually did not do so. Thus, in case 1 there is a history of an acute cerebral disease two days after birth. In case 2, the child seemed to have been normal up to the end of the third month. In case 3, there was a definite indication of the disease beginning in the fifth year, following a two months' illness. In case 4, the patient was normal up to 1 year, when the disease began following an attack of measles.

3. The location of the status marmoratus was not uniform. In the first two cases it was apparently restricted to the basal ganglia. In the third, however, the basal ganglia were free from it, the main seat of the process being in the cortex.

4. Besides the status marmoratus there was in all three cases a widespread disease of a number of regions of the brain.

5. In each of our cases the clinical and pathologic observations indicated a disease process, although there is nothing to prove that the etiologic factor was the same in all cases.

The assumption of a developmental anomaly as the fundamental substratum could not be justified, because the different structures seemed to have been affected after they had fully developed. Pathologically, the pictures suggested a progressive lesion. In case 2, there were definite indications of an old inflammatory (encephalitic) lesion. In case 3, the whole pathologic condition developed around a vascular lesion, which was probably inflammatory. In case 1, too, the histologic picture pointed toward the existence of an inflammatory process. In case 4, the disease had its onset following an attack of measles, which certainly suggests a postinflammatory process.

The cases described by C. and O. Vogt,[1] which they used as the basis of establishing the syndrome, show some factors that would speak against their conclusions that the disease was a congenital system disease. Thus one finds, in a number of these cases, the statement that the symptoms were present in early childhood, without making it clear as to whether this means that they had been noticed soon after birth or following a free interval. The reports reveal a tendency toward clinical progression, and the neurologic findings point to a widespread lesion. It is difficult to understand how one could restrict the process to an involvement of one particular system. In a lesion that is regarded as primarily "pathoklitic" and developmental in origin, one finds it difficult, if at all possible, to account for the occurrence of such findings as hydrocephalus, accumulations of gitter cells (which the Vogts themselves thought pointed toward an inflammatory process) and glial scars.

All these points gain particular importance when one considers them in the light of reports by other authors. Scholz [5] described a case in which the patient showed a normal development up to 11 months of age. The signs of the disease then came on after an acute encephalitic attack.

In Bielschowsky's observation, also, there was a development of mental defectiveness, spasticity and inability to walk or stand following a febrile attack in infancy.

Onari [6] in his report emphasized the variations in this process and suggested the possibility of different etiologies, developmental, acquired or both. Of further interest are the reports by Meyer [4] and Pfeiffer.[7] Meyer reported a case in which the lesion, not unlike that in our case 3, developed around a vascular disease of an endarteritic type. Pfeiffer found the development of this lesion to have occurred on the basis of a birth injury in the sense of Schwartz.[8]

All of these considerations point to these conditions as acquired processes. In our own cases we feel justified in assuming that they were encephalitic. The clinical histories in cases 3 and 4 speak definitely for such an assumption. In case 2 we know only that symptoms began at the age of 3 months, and in case 1 we have the history of a "cerebral hemorrhage." In both of these cases, however, as well as in case 3, the histologic findings show distinct marks of an old encephalitic process that has run its course.

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6. Onari, K.: Ueber zwei klinisch und anatomisch kompliziert-liegende Fälle von Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:457, 1925.

7. Pfeiffer, F.: Choreathetose bei Littlescher Lähmung, Arch. f. Psychiat. **72**: 728, 1928.

8. Schwartz, P.: Erkrankungen des Zentral-Nervensystems nach traumatischer Geburtsschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:263, 1924.

As to the nature of the encephalitis in question, we would provisionally place it in the type 2 of Spatz,[9] i. e., the metastatic focal encephalitis, with foci in the cortex, white matter and basal ganglia. The pathologic pictures of all our cases fit in this group quite well. We are, of course, aware that one cannot speak with absolute certainty in cases of this type after the acute inflammatory process has run its course.

If we regard the whole process, then, at least in the majority of cases, as having developed on the basis of an inflammatory process, there still remains the question as to how and why the myelinization of the glial scars takes place. Three possibilities have been advanced. Scholz [5] was of the opinion that there is an actual regeneration of axis cylinders; Bielschowsky thought that it was a myelinization of preexisting naked axis cylinders, and Meyer [4] advanced the view that it was a purely mechanical condensation of preexisting, preserved myelinated nerve fibers. Meyer argued that he noticed no definite signs of regeneration, and, furthermore, he could not conceive of such a process in this particular lesion. He could not, however, explain the actual increase in quantity of the medullated fibers in tissues in which they are normally rather scanty on a simple mechanical basis. Both our cases and the one described by Scholz [5] show definite manifestations of regeneration in the loops, ravelings and bulbs which, even if not numerous, are nevertheless distinct. The possibility of regeneration under more or less similar circumstances in the central nervous system was, furthermore, shown conclusively by the experimental work of Borst.[10] The newly formed fibers described by Borst have even shown the same characteristic deviation from the normal that we have noticed in our cases, in consistency, shape, staining quality and arrangement.

The reason why this myelinization of glial scars is so rarely encountered must be looked for in the special stage of development during which the lesion occurs. Spatz [9] has shown that this is particularly apt to occur during infancy, a period which in this respect differs from both the fetal and the later stages of life. It is on this basis, too, that we can agree with Hallervorden [11] in his opinion that the myelinization of the glial scar, responsible as it is for the morphology of the status marmoratus, is really not fundamental in its pathogenesis. Hallervorden thus regarded the myelinization of the glial scars as incidental, and even advanced the possibility of the paradoxical occurrence

9. Spatz, H.: Encephalitis, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

10. Borst, M.: Neue Experimente zur Frage nach der Regeneration im Zentral-Nervensystem, Beitr. z. path. Anat. u. z. allg. Path. **36**:1, 1904.

11. Hallervorden, J.: Die extrapyramidalen Erkrankungen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

of a status marmoratus without myelinization. It is true, of course, that the mechanical conditions introduced by the development of the scars influence the peculiar arrangement of the fibers, but we cannot agree, in view of the previous discussion, that they are the only factors and that the myelinization is only apparent.

In the clinical evaluation of this syndrome, the establishment of a clearcut clinical entity that could cover all cases of status marmoratus appears to be neither possible nor desirable. The fact that the process is not limited to the striate body but may affect practically every region in the brain would necessarily rule out a uniform neuropsychiatric picture. A certain number of cases, however, show definite points of contact. The frequency of an encephalitic process as the starting point, the onset at a certain age level, the predominance of extrapyramidal symptoms and the originally progressive nature of the process which afterward tends to become stationary form a nucleus for a syndrome. We are well aware that this does not completely establish the syndrome, but it gives a working method by which one may approach the problem, unhampered by the fetters imposed by the name.

SUMMARY

1. Four cases are presented, in three of which postmortem examinations showed, among other lesions, the presence of status marmoratus; in the fourth case, the clinical picture and history were typical of the syndrome described under that name.

2. In these cases the important features were:

(*A*) There were a negative family history and a normal interval between birth and the onset of the disease.

(*B*) The clinical history of the onset of the disease and the histologic picture showed that the disease developed on the basis of an encephalitic process, most probably acquired.

(*C*) The involvement was widespread, affecting the cortex as well as the basal ganglia, while in one of the cases the status marmoratus was present in the cortex and not in the ganglia.

3. In view of these findings and a number of similar data reported by other observers, the original concept of the nature of this disease will have to be revised.

AMYOTROPHIC LATERAL SCLEROSIS

COMPLICATED BY SUBACUTE COMBINED DEGENERATION OF THE CORD: CLINICAL AND PATHOLOGIC REPORT OF A CASE

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Subacute combined degeneration of the cord and amyotrophic lateral sclerosis are distinct morbid entities, each possessing a pathologic picture of its own. In the former, the histologic changes are represented by degeneration of the posterolateral columns; in the latter, by that of the corticomuscular system of nerve fibers, extending from the motor cortex through the spinal cord and peripheral nerves to the muscles. In subacute degeneration of the cord the process is a so-called primary degeneration, originating in the nerve fibers themselves; in amyotrophic lateral sclerosis the degeneration is secondary, originating in the motor ganglion cells of the cortex, medulla and anterior horns of the spinal cord. While either condition in its typical and uncomplicated form offers no diagnostic difficulties, it is not so in cases that, like the one presented here, are atypical and complicated.

REPORT OF CASE

Clinical History.—An Italian man, aged 48, with a good personal and family history, entered the Cook County Hospital (service of Dr. Yudelson) on Jan. 17, 1930, because of inability to walk and rigidity of the left upper extremity. The patient had been in good health prior to February, 1929, when he began to experience weakness and tremor in the left foot. The weakness soon involved the right foot, and both legs, and after four months extended to the upper extremities, rendering the patient helpless. About three and one-half months prior to his entrance to the hospital, the patient had undergone a laminectomy which did not cause any improvement.

Examination.—The patient appeared poorly nourished; he was hardly able to move the upper or lower extremities; passive movements were spastic and thus greatly restricted. Over the dorsal region a large scar was present, from a laminectomy performed evidently for the spastic gait.

The musculature was atrophied throughout, especially in the extremities which were spastic. The speech was indistinct, thick and slurring; the tongue could not be protruded beyond the teeth, was atrophied and exhibited fibrillary twitchings.

Read before the Eighty-Third Annual Meeting of the American Medical Association, New Orleans, May 12, 1932.

From the Neurologic Service of Cook County Hospital and the Neuropathology Laboratory of the University of Illinois College of Medicine.

The pupils reacted normally both to light and in accommodation; the tendon, ulnar, radial and mandibular reflexes were normal, without Babinski, Chaddock or Oppenheim signs, but ankle clonus was present bilaterally; the abdominal and cremasteric reflexes were absent; the corneal, nasal and pharyngeal reflexes were normal.

Sensibility: This was impaired over the "mediolateral aspect of the thighs"; on the left foot and leg the patient "could not differentiate between sharp and dull."

Course.—During the patient's eighteen months' stay in the hospital, the condition grew steadily worse. The emaciation and rigidity progressed; the tongue and the muscles of the face and extremities exhibited marked atrophy; the acts of chewing and swallowing became practically impossible and the speech entirely unintelligible; the joints of the upper and lower extremities became very rigid and, in the

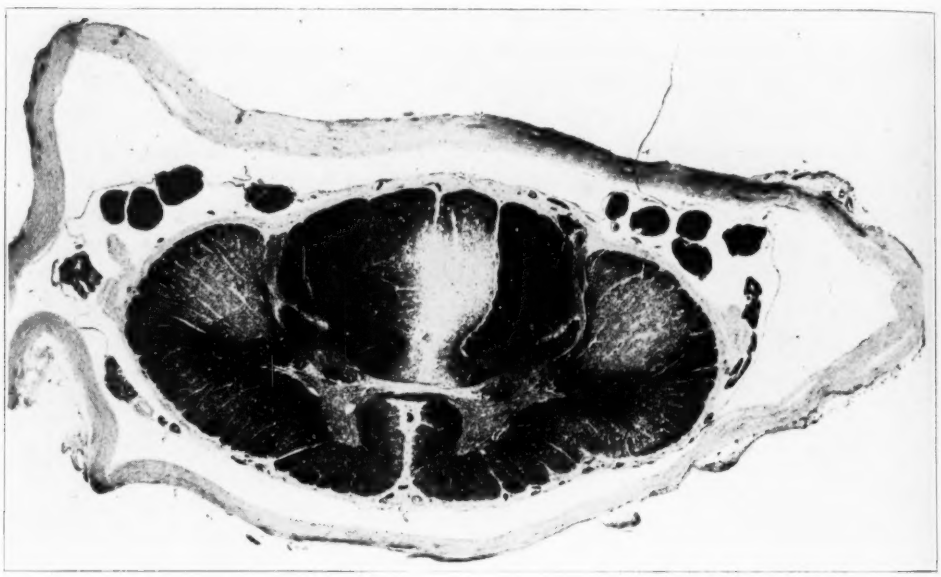

Fig. 1.—Upper dorsal segment (approximately the fourth). The columns of Goll, the lateral and anterior pyramids, the dorsal spinocerebellar tract of Flechsig on the right are degenerated. The myelinated fibers of the columns of Clarke, and to a lesser extent of the anterior horns, are well preserved. Weigert-Pal; reduced from × 15.

later stages of the disease, it was not possible to obtain the tendon reflexes. The hands were in a state of main en griffe and, like the rest of the joints, were rigid and immobile. The cardiovascular and genito-urinary systems were normal. The pulse rate was 84, the respiration rate 24 and the temperature 98 F.

Laboratory Data.—The urine was normal; the Wassermann reaction of the blood was negative; the spinal fluid could not be examined as a spinal puncture was unsuccessful. No records were found in reference to a differential count of the blood or the conditions of the gastric activity. Probably such laboratory examinations were considered unnecessary, as the clinical picture of amyotrophic lateral sclerosis was unquestionable and the general condition was too poor for gastric or similar studies.

The patient died two and one-half years after the onset of the illness.

Pathologic Observations.—The brain and spinal cord were studied with the following methods: Weigert-Pal and its modifications (for myelin fibers), Herxheimer and Marchi (for fat), Alzheimer-Mann, Holzer, Cajal and Hortega (for glia), the Bielschowsky silver method (for axons and neurofibrils) and also the combined staining methods of Marchi-Alzheimer and Bielschowsky-Alzheimer for the study of various phases of secondary degeneration.

Macroscopic observations of the spinal cord showed no abnormalities, except for a marked reduction in size at all levels.

Microscopic examination revealed changes in both the white and gray substances. In the former, they showed as degeneration of various tracts in the posterior and lateral columns, mainly the pyramidal fibers and the columns of

Fig. 2.—The fourth cervical enlargement. The changes are practically similar to those reproduced in figure 1, but the degeneration also involves the columns of Burdach, the tracts of Flechsig (especially on the right), Helweg (*H*) on the left and a major portion of the posterior limb of the lateral limiting zone. Myelinated fibers in the anterior cornua are sparse; the anterior commissure, the entrance root zone and the posterior roots are not affected. Weigert-Pal; reduced from × 15.

Goll (fig. 1). The pyramidal tract degeneration extended from the cervical to the lumbosacral region; that of the columns of Goll involved the cervical (figs. 2 and 3), the dorsal (fig. 1) and partly the lumbar areas, while in the sacral portion it showed only a mild rarefaction (fig. 4) of the dorsal columns. The degeneration of the columns of Goll extended to the posterior commissure and reached the pia, but was usually separated from the latter by a broad, well preserved area (fig. 1). At some levels (fig. 2) the columns of Burdach were invaded, without involvement of the posterior roots or their entrance zone.

Aside from the lesion of the pyramidal fibers and the columns of Goll, the spinal cord also showed degeneration of the tract of Helweg (fig. 2), and some invasion of the lateral limiting zone and of the tracts of Flechsig (especially in specimens stained with scarlet red) (fig. 3). The accompanying photomicrographs show the much greater extent of the degeneration in the posterior than in the lateral columns, and the absence of the areolar or spongelike appearance of the degenerated areas so often seen in subacute combined degeneration of the cord. Such areas, however, could be made out, mainly in the lateral columns, when they were stained with the silver method of Bielschowsky (fig. 5) or that of Holzer (fig. 6). With the former method one could also see preserved axons in areas apparently totally devoid of nerve tissue, while with other staining methods—toluidine blue and van Gieson—these barren, pale areas exhibited the presence of

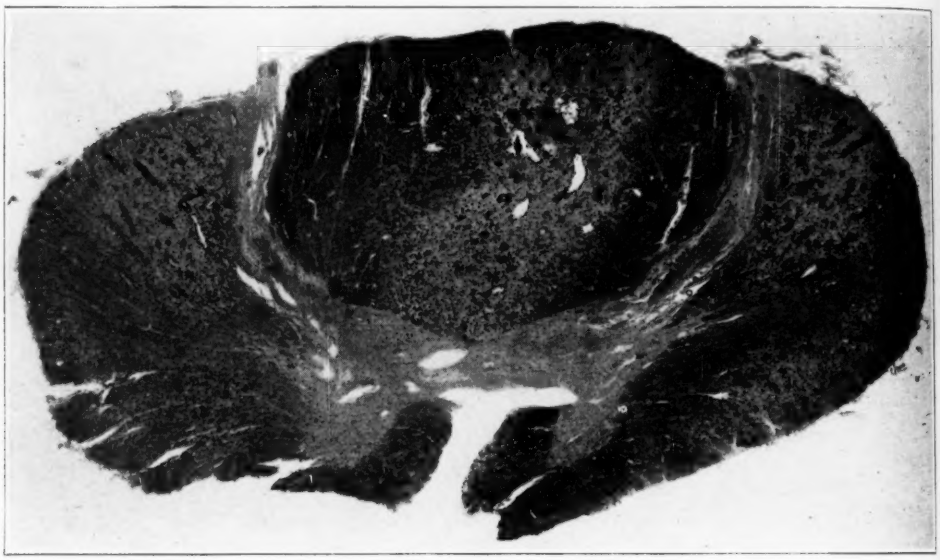

Fig. 3.—Section of the same level as that shown in figure 2, stained with scarlet red. The black streaks are blood vessels infiltrated with fat granule bodies.

numerous blood vessels, surrounded, cufflike, by circular layers of fat granule bodies (fig. 7) and also numerous cytoplasmic glia (macroglia) cells.

In contrast to so vast a degeneration of the spinal cord, the changes in the medulla, midbrain and regions higher up were insignificant. The medulla exhibited a slight involvement of the pyramids which appeared normal in the pons, peduncles and internal capsule. Only in sections stained with toluidine blue was it possible to see scattered spots of nerve degeneration evidenced by a marked glial reaction, proliferation of glia nuclei and formation of cytoplasmic glia.

The anterior horns were greatly reduced in volume and exhibited, for the most part in the cervical and sacral regions, a scarcity of myelinated nerve fibers and a marked reduction in the number of ganglion cells. These were all invariably changed in form and size; they showed phenomena of satellitosis and neuronophagia, and were replaced by cytoplasmic glia cells (astrocytes) and glia fibers. In many instances, the anterior horns appeared as a glia-tissue scar which

undoubtedly was responsible for their shrunken disfiguration and reduced size. The posterior horns also appeared thinned and, like the rest of the spinal cord, reduced in size. The ganglion cells of the basal half were diminutive (fig. 8) and devoid of chromatin; the dendrites were tortuous, tumefied and, like the cell bodies, homogeneous. Some ganglion cells were granular, as if broken up or liquefied. The glia tissue was fibrillar, and showed astrocytes and an increased number of blood vessels. The changes were evident in the thoracic region, but were absent in the lumbosacral.

Fig. 4.—Third sacral segment. Slight pallor of the columns of Goll and of Flechsig's tract. In the left anterior horn myelinated fibers are retained (at *P L*) in the posterolateral area. Hardly any groups of ganglion cells are in evidence. Weigert-Pal.

Analogous changes were present in the motor nuclei of the bulbar nerves (fifth, tenth and twelfth) (fig. 9), the nuclei of the posterior longitudinal bundles and the motor cortex. The twelfth nucleus was especially changed (fig. 9). Like the ganglion cells of the anterior horns, the nucleus was largely replaced by dense glia tissue and also numerous blood vessels, while the twelfth nerve itself was hardly discernible. No ganglion cell changes were found in the basal ganglia; in the pons they were mild, but in the cortex they were analogous to those of the anterior horns and the nuclei of the motor bulbar nerves. The Betz cells were absent; the

large pyramidal cells showed phenomena of satellitosis and neuronophagia, and the layers of the motor cortex were generally very cellular.

In contrast to manifest changes in the motor cortex of the brain, medulla and cord, no changes were present elsewhere in the central nervous system. Thus, the columns of Clarke (fig. 1) and the posterior horns contained well developed, myelinated nerve fibers and normal ganglion cells, with the exception of a few that were degenerated at their base as already mentioned. The posterior root fibers (fig. 2) were well developed in contrast to the anterior roots, in which nerve fibers were scarce and on the whole appeared atrophied (fig. 2). Nor were ganglion cell changes present in the areas of the brain outside the motor region, for instance, in the parietal, temporal and occipital lobes.

Fig. 5.—Longitudinal section of the lateral columns. The areolar appearance is due to the presence of numerous gitter cells and blood vessels encircled by collars of the former. The rest of the picture is made up of fibrillary glial tissue and many glial nuclei. Bielschowsky stain; reduced from × 118.

The affected regions invariably presented reactive glial phenomena. As I have already pointed out, in the gray matter of the spinal cord and medulla the reaction was in the form of cytoplasmic glia and the formation of a glial scar and of new blood vessels. In the white substance of the spinal cord (the lateral and posterior columns) the reactive changes were similar to those described in various stages of secondary degeneration, from the breaking down of the nerve fibers, with the formation of Marchi globules, to their transformation into various forms of gitter cells.

Of still greater interest were the changes in the subarachnoid space. These may be designated as an aseptic meningitis; the cells were histiocytes packed with pigment, fibroblasts, mesothelial and gitter cells, with a few lymphocytes and no plasma cells.

Summary of Pathologic Data.—These may be summed up as degeneration of the central and peripheral motor nerve fibers, including the cells of their origin—cortical, bulbar and spinal; of some cells of the posterior horn, and of the posterior columns, mainly those of Goll, with phenomena of so-called aseptic meningitis.

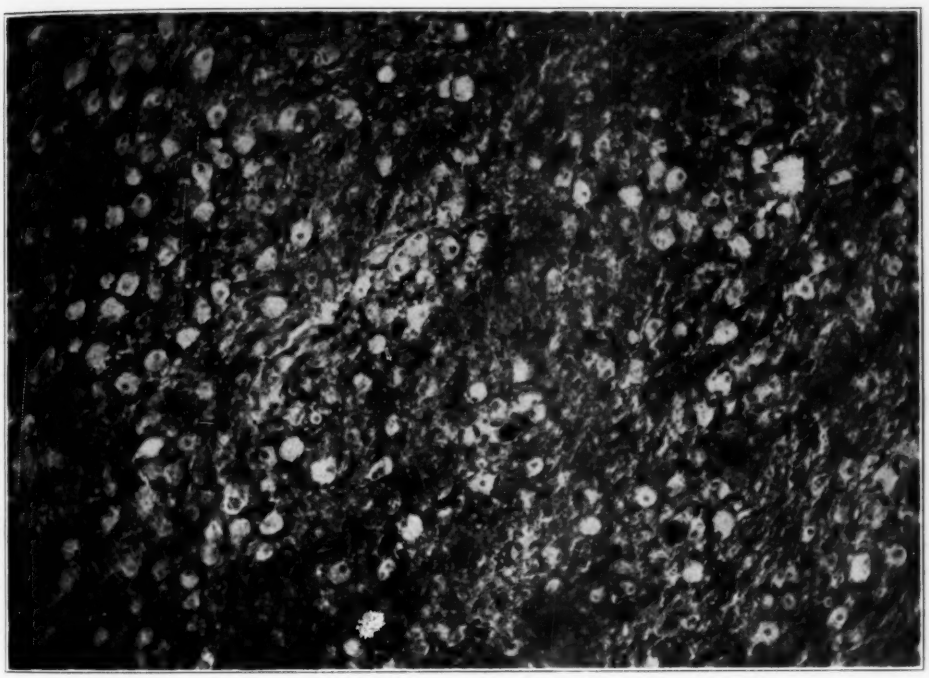

Fig. 6.—The areolar appearance in this picture is due to swelling of the myelin nerve sheaths. The majority of the axons and myelin fibers are retained; in some places they have fallen out, leaving the empty vacuoles that are so common in subacute combined degeneration of the cord. Holzer's stain; reduced from × 250.

COMMENT

The pathologic data outlined justify a diagnosis of amyotrophic lateral sclerosis complicated by a degeneration of a sensory tract of fibers, the columns of Goll, and, to a lesser extent, of those of Burdach. The first impression that one gains from a study of the photographs of the stained spinal cord sections (figs. 1, 2, 3 and 4) is that one is

dealing here with a subacute combined degeneration of the cord. Such a diagnosis would be suggestive, were it not for the concomitant involvement of the anterior horns. Though the latter has been described by Gordon Holmes [1] in a combined sclerosis of the posterolateral columns and by Stone [2] and others, in subacute combined degeneration of the cord, the changes in general are not only rare but mild. Nor do they attain the extent and intensity seen in the present case. In other words, one is not justified to assume that my case, which clinically was one of

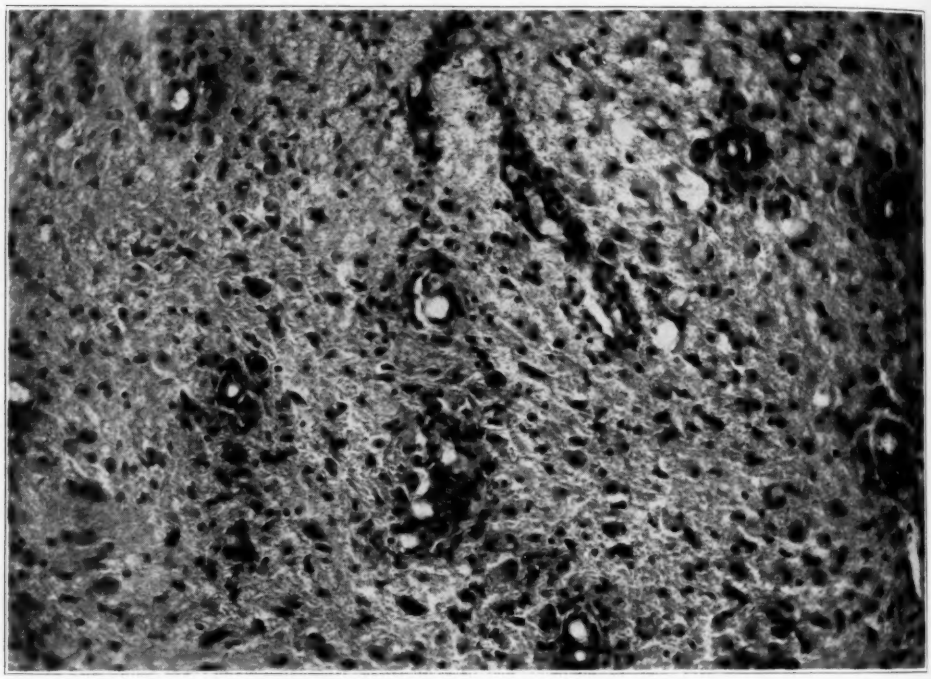

Fig. 7.—Degenerated Goll's columns stained with toluidine blue. The dark rings are blood vessels infiltrated with fat granule bodies and are scattered over a field of scar tissue; reduced from × 250.

a typical amyotrophic lateral sclerosis, was pathologically one of an atypical subacute degeneration of the cord combined with atrophy of the anterior horns. On the other hand, cases of amyotrophic lateral sclerosis have been reported in which disturbances of sensibility were

1. Holmes, Gordon: A Case of Combined Degeneration of the Spinal Cord with Amyotrophy, Rev. Neurol. & Psychiat. **11**:76, 1913.

2. Stone, T. T.: Subacute Combined Degeneration of the Spinal Cord with Chronic Changes in the Anterior Horns of the Cervico-Dorsal Region, J. Nerv. & Ment. Dis. **73**:41, 1931.

evident (Moeli,[3] Oppenheim,[4] Hektoen,[5] Pilz,[6] Dercum and Spiller,[7] Lejonne and Lhermitte,[8] Anglada[9] and others). In these it is rather curious that, marked as they were in some cases, the histologic changes were either mild or absent. For instance, in the cases of Anglada,[9] and Wechsler, Brock and Weil[10] the sensory manifestations were so prominent that a diagnosis of tumor of the cauda equina was made and a laminectomy was even performed (case of Wechsler and associates). With the change of the clinical picture, a diagnosis of amyotrophic lateral sclerosis was made and confirmed by necropsy. This, however, revealed no changes in the posterior columns. Nor were they present in the patient of Anglada,[9] while in a large number of other cases the changes were only mild. Thus, in the case of von Czylarz and Marburg[11] they were present as a slight pallor of the cervical and upper portions of the dorsal columns; they were somewhat more intense in the cases of Moeli,[3] Charcot and Marie,[12] Oppenheim[4] and Hektoen.[5] However, in the cases of Gordon Holmes[1] and especially in the case of Babonneix and Widiez[13] the anatomic changes did resemble those observed in my case. The patients of Babonneix and Widiez, for instance, exhibited atrophy of the small muscles of the hands with paresis of the muscles of the shoulder and bulbar phenomena (dysphagia, nasal speech, difficulties in chewing and fibrillary twitchings of the tongue),

3. Moeli, C.: Ein Fall von amyotrophischer Lateralsklerose, Arch. f. Psychiat. **10**:718, 1879.

4. Oppenheim, H.: Zur pathologie der chronischen atrophischen Spinallähmung, Arch. f. Psychiat. **24**:758, 1892.

5. Hektoen, L.: Amyotrophic Lateral Sclerosis with Bulbar Paralysis and Degeneration in Goll's Columns: A Contribution to the Pathology of the Primary Combined Systems, J. Nerv. & Ment. Dis. **20**:145, 1895.

6. Pilz, Alexander: Ueber einen Fall von amyotrophischer Lateralsklerose, Jahrb. f. Psychiat. u. Neurol. **17**:221, 1898.

7. Dercum, F. X., and Spiller, W.: A Case of Amyotrophic Lateral Sclerosis Presenting Bulbar Symptoms, with Necropsy and Microscopic Examination, J. Nerv. & Ment. Dis. **26**:84, 1899.

8. Lejonne, P., and Lhermitte, J.: Un cas de sclérose amyotrophique à forme anormale avec autopsie, Rev. neurol. **14**:485, 1906.

9. Anglada, J.: Sclérose latérale amyotrophique ascendante avec manifestations douloureuses et paraplégie en fléxion intense, Montpellier méd. **32**:73, 1911.

10. Wechsler, I. S.; Brock, S., and Weil, A.: Amyotrophic Lateral Sclerosis with Objective and Subjective (Neuritic) Sensory Disturbances: A Clinical and Pathologic Report, Arch. Neurol. & Psychiat. **21**:299 (Feb.) 1929.

11. von Czylarz, E., and Marburg, O.: Beiträge zur Histologie und Pathogenese der amyotrophischen Lateralsclerose, Ztschr. f. klin. Med. **43**:59, 1901.

12. Charcot, J. M., and Marie, P.: Deux nouveux cas de sclérose latérale amyotrophique suivis d'autopsie, Arch. de neurol. **10**:1 and 168, 1885.

13. Babonneix, L., and Widiez, A.: Sclérose combinée: lésions diffuses et inflammatoires du névraxe. Anévrysme de l'artère spinale antérieure. Syphilis probable, Rev. neurol. **1**:1214, 1930.

with exaggerated tendon reflexes but without a Babinski sign and disturbances of sensibility. The histologic changes, which were studied by Lhermitte, showed marked "sclerosis" of the crossed and direct pyramidal tracts and columns of Goll, combined with considerable diminution of the number and decrease in the volume of the cells of the anterior horns and the nucleus of the twelfth nerve. Demyelination was also present in the pyramidal fibers of the medulla and peduncles in the mesial fillet. In addition, changes were found in the Purkinje cells and the granular layer of the cerebellum, and the anterior spinal artery contained

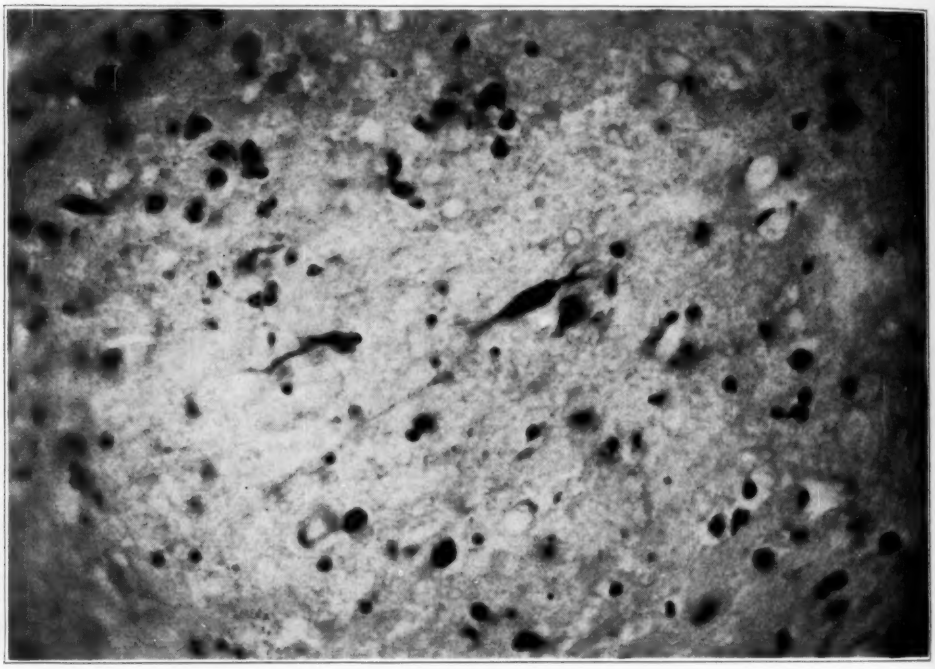

Fig. 8.—Ganglion cell changes in the posterior horns, described in the text. Toluidine blue; reduced from × 470.

an aneurysm. Notwithstanding such evident changes in the spinal cord, repeated clinical examinations did not even suggest subacute or any other combined degeneration of the cord, but syphilis was strongly considered as the cause of the changes in this case and of amyotrophic lateral sclerosis in general.

Without discussing the nature of amyotrophic lateral sclerosis, considered by some as an inflammatory process and by others as a form of neurosyphilis, I wish merely to emphasize that in my case the inflammatory phenomena were insignificant. A few lymphocytes were occasionally encountered and were most likely secondary to the presence

of the vast amounts of degenerative products; that is, they were a manifestation of a so-called sympathetic inflammation. The changes were decidedly degenerative, as is usually seen in both amyotrophic lateral sclerosis and subacute combined degeneration of the cord. The fact that the degeneration was much more advanced in the columns of Goll denotes that here the disease probably began earlier than in the motor fibers. If such is the case, one is forced to the conclusion that the causative factor—endotoxins—responsible for subacute combined degeneration of the cord may also be a cause of amyotrophic lateral sclerosis,

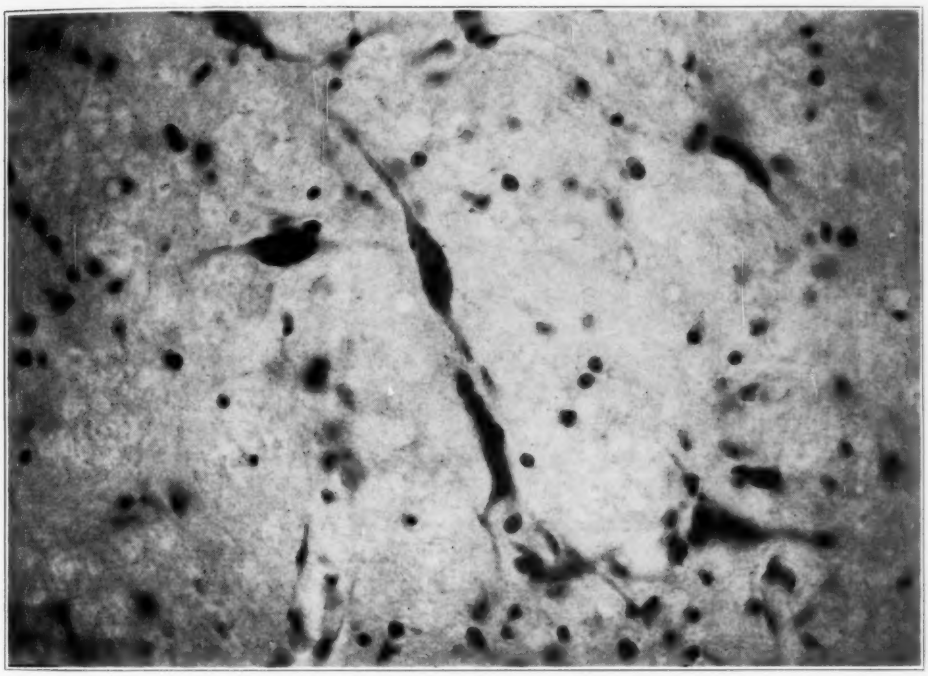

Fig. 9.—Various degenerated cells of the nucleus of the twelfth nerve, described in the text. Toluidine blue; reduced from × 520.

and that the two conditions may be combined. In favor of my case being a combination of the foregoing two degenerative conditions speaks the involvement of other tracts (Burdach's and Flechsig's) which are usually involved in subacute combined degeneration of the cord, and spared in amyotrophic lateral sclerosis. The degeneration of the posterior columns and the reactive glial phenomena in my case certainly more resembled those seen in subacute combined degeneration of the cord than those seen in tabes, syphilis, vascular sclerosis and the degeneration of so-called columnar cells. All these conditions were mentioned

as the possible causes of degeneration of Goll's columns in amyotrophic lateral sclerosis.

Whatever the character of the changes and their possible cause, they cannot very well explain the patches of anesthesia in my patient or the pain mentioned by various observers. One is tempted to ascribe the cause of the objective and subjective disturbances to the involvement of the basal portion of the posterior horns, which is contiguous with the much damaged anterior horns and which gives origin to the spinothalmic tracts, the conductors of pain and temperature. However, in my case the posterior horn changes were marked, not in the lumbosacral, but in the thoracic region of the cord; these changes have rarely been described in amyotrophic lateral sclerosis.[1] It is obvious that further observations along these lines are necessary.

CONCLUSIONS

1. Amyotrophic lateral sclerosis, essentially a motor nerve disorder, clinically may show sensory disturbances.

2. Pathologically, it may be associated with degeneration of the sensory tracts, suggesting a combination with subacute combined degeneration of the cord.

3. From the extent and intensity of the degeneration, one may assume that one morbid process arises after the other, both being caused by the same as yet unknown factor.

4. The basal portions of the posterior horns of the gray matter of the spinal cord may be a part of the pathologic picture in atypical cases of amyotrophic lateral sclerosis and be responsible for the subjective and objective sensory disturbances occasionally observed in this morbid condition.

ABSTRACT OF DISCUSSION

Dr. Theodore T. Stone, Chicago: I agree with Dr. Hassin that the clinical picture of this case is that of amyotrophic lateral sclerosis and that the pathologic picture is amyotrophic lateral sclerosis associated with changes in the posterior columns of the spinal cord. Most of the severe changes in this case appear in the anterior horns as well as in the cortical and bulbar areas. The pathologic changes described by Dr. Hassin as occurring in the anterior horns are typical of amyotrophic lateral sclerosis. The mild changes described in the posterior columns are suggestive of subacute combined degeneration of the cord.

In January, 1931, I reported a case of subacute combined degeneration of the cord with chronic changes in the anterior horns of the cervicodorsal region. In this case the neurologic findings, blood picture and gastric analysis all pointed to a combined lesion of the cord and pernicious anemia. In addition, this patient had atrophy of the small muscles of the hand. The pathologic picture found was not like that described by Dr. Hassin. The posterolateral columns showed severe vacuolation, degeneration of axis-cylinders and myelin sheaths, reactive glial phenomena and regressive glial changes, so that in the periphery of the posterior

columns definite evidence of gliosis was seen. There were no changes in the pachymeningeal or leptomeningeal spaces. The changes in the anterior horns were confined to the cervicodorsal region and were of a mild nature showing chronic degenerative changes in the ganglion cells with a reduction in the number of the cells in this region. No evidences of glial reaction, satellitosis or neuronophagia were found. The fibers of the anterolateral bundle were definitely degenerated.

It is entirely possible, I believe, that an endogenous toxin might cause the changes described in the essayist's paper and produce a degeneration of either the central and peripheral motor nerve fibers or those of the posterior columns or both.

It seems extremely important that in the future all cases of subacute combined degeneration of the cord and amyotrophic lateral sclerosis receive an intensive study both clinically and pathologically. By making a careful neurologic examination one may find other objective evidence which otherwise might be overlooked. By making a complete histologic study of the entire spinal cord as well as of the brain with the more important stains, one may find changes in one part of the cord that are not present in another part. In this way the solution of our present enigma may be determined.

Dr. Walter Schaller, San Francisco: Amyotrophic lateral sclerosis is often associated with degeneration of the posterior column of the cervical region. I have seen such cases. In a discussion of amyotrophic lateral sclerosis, according to the symposium during the Charcot centenary, that was well brought out.

This thought led me to try liver therapy in amyotrophic lateral sclerosis, but I am sorry to say without any results. The data shown us were beautifully worked out and typical of combined degeneration in the phagocytic cells and vacuolization of the cord, but were not typical of the situation according to my experience. I found that the degeneration of the cord, in the posterior columns, is particularly marked, in subacute combined sclerosis, in the dorsal and the lumbar cord. Here it obviously was not.

It occurs to me that possibly in Dr. Hassin's case we are dealing with amyotrophic lateral sclerosis with intensification of changes in the posterior region of the upper part of the cord. I think that it is doubtful whether there is a common toxin to account for these conditions.

Dr. Walter Freeman, Washington, D. C.: I should like to endorse Dr. Schaller's discussion. Dr. Hassin evidently bases his interpretation of the case as a combination of two diseases on finding degeneration in the posterior column. This has been reported previously in cases of undoubted amyotrophic lateral sclerosis. I think that before a diagnosis of a combination of diseases can be made, further efforts to establish the presence of subacute combined degeneration should be made.

In rather rapidly advancing cases of amyotrophic lateral sclerosis one may find vacuolation and fat release in the lateral column. According to French and Belgian authorities, particularly van Bogaert, one may find this also in the posterior columns.

I should like to ask Dr. Hassin whether any changes were found in the viscera that would indicate the presence of a pernicious anemia, such as lesions in the spleen or liver.

Dr. Henry R. Viets, Boston: I think that this contribution of Dr. Hassin's is of unusual interest. I rather feel, however, with the other two men who discussed the paper that certain of these findings are not so uncommon and that one does not feel justified in making a diagnosis of combined degeneration without having good clinical evidence that such is the case. It would seem to me that we

need here more definite clinical evidence of subacute combined degeneration before we can be sure that this is anything more than Charcot's disease plus certain changes that are often seen in cachexia.

Dr. George B. Hassin, Chicago: As I mentioned, Dr. Stone reported a case of subacute combined degeneration of the cord in which the anterior cells were atrophied. Such cases are unusually rare, and when one is confronted with a case like mine or like that of Dr. Stone, one does not know whether one deals with subacute combined degeneration complicated by atrophy of the cells of the anterior horns, with amyotrophic lateral sclerosis complicated by subacute combined degeneration of the cord or with a condition that as yet has not been described.

Those who discussed my paper did not help to solve the problem. They could not explain the exceptionally extensive degeneration in the spinal cord, which, had atrophy been absent, would have been diagnosed by every one as subacute combined degeneration of the cord. It would probably be simpler to consider the case as some authors, like Gordon Holmes, Lhermitte and others did, as one of amyotrophic lateral sclerosis associated with a combined sclerosis. Combined sclerosis does not mean subacute combined degeneration, but a widespread degeneration, usually of obscure etiology, involving the white matter of the cord and of which subacute degeneration of the cord is one of the forms. I consider my case to be that of amyotrophic lateral sclerosis associated with subacute combined degeneration because of the histologic features and the typical distribution of the changes. One does not find them in the stage of cachexia, nor were such extensive degenerations of the posterior columns recorded in amyotrophic lateral sclerosis.

As to the region of the cord preferably affected in subacute combined degeneration of the cord, it is the dorsal, which here is much more involved than any other region.

There was no evidence of disease in the body of the patient. His condition was so wretched that it was impossible to make a gastric examination. On the other hand, the clinical picture was that of classic amyotrophic lateral sclerosis. His tongue was completely atrophied, bulbar symptoms were marked and were associated with pronounced spasticities and contractures, but not a single thing suggested clinically a subacute combined degeneration of the cord. Lhermitte reported, in 1931, changes in a case exactly similar to mine. He spoke of a combination of some changes in the cord but did not specify them. Nor were there in other similar cases any discussions as to the nature of the changes in the spinal cord. I think that the explanation I offer, that of a combination of two diseases caused by one unknown factor, seems to be the best.

EFFECT OF "HABITUATION" ON BLOOD PRESSURE IN SCHIZOPHRENIA

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WORCESTER, MASS.

In a previous publication,[1] the basal blood pressures in a group of male schizophrenic patients at the Worcester State Hospital were found to be significantly lower than those of a larger group of normal subjects (medical students). The values for the patients were 104 mm. systolic and 54 mm. diastolic as compared with the students' levels of 115 mm. systolic and 71 diastolic.

Since the writing of that paper, the patients on the Research Service have been confronted with a novel situation, resulting in a change in their blood pressures which has persisted, thus determining a new average level.

MATERIAL AND METHODS

This situation is the establishment of a series of complex test procedures, enduring over a period of one month and repeated twice, on each occasion being succeeded by an interval of rest of two months, with the purpose of determining the variability of the results and the constancy of their fluctuation from the normal. Among these procedures are four determinations of the rate of oxygen consumption ("basal metabolism"), on which occasions the basal blood pressure is obtained. Consequently there are for each patient three groups of four blood pressure readings with an interval of two months between each set. The presentation and discussion of these data form the basis of the present paper.

The group under consideration comprises a relatively small number, 50 cases, but is one which has been studied under carefully controlled conditions. The subjects varied in age from 20 to 40 years and had been confined in the hospital for from two months to twenty-one years. So far as exhaustive clinical and laboratory investigations could determine, they were suffering from no organic disease. They constituted essentially a "pure culture" of schizophrenia from the physical point of view. The circumstances under which the pressure determinations were made were unusual, in that each patient was undergoing one or more test procedures each day and was kept in a state of constant activity, quite unlike anything that he had previously experienced. The patients thus became thoroughly habituated to laboratory procedures. Their reactions to this series of tests, from the point of view of blood pressure, is summarized in the accompanying table.

From the Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School, and the Worcester State Hospital.

1. Freeman, H.; Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia, Arch. Neurol. & Psychiat. **27**:333 (Feb.) 1932.

In order to bring out more distinctly any variations that might be demonstrated, the blood pressure readings in each period were subdivided as follows:

Lowest blood pressure: the lowest pressure in the series of four readings on each patient.

Highest blood pressure: the highest pressure in the series of four on each patient.

Mean blood pressure: the mean of each group of readings on each patient.

All observations: all blood pressure readings brought together in one frequency distribution.

Systolic and Diastolic Blood Pressures of Fifty Schizophrenic Patients During the Three Periods of Study

	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation, per Cent
Systolic blood pressure						
Lowest						
1st period	67	122	55	95.2 ± 1.20	12.60 ± 0.85	13.2
2d period	67	122	55	91.1 ± 1.21	12.67 ± 0.85	13.9
3d period	40	122	82	90.8 ± 1.19	12.45 ± 0.84	13.7
Highest						
1st period	82	152	70	116.1 ± 1.53	15.98 ± 1.08	13.8
2d period	87	142	55	107.1 ± 1.24	12.98 ± 0.88	12.1
3d period	82	152	70	111.1 ± 1.49	15.65 ± 1.06	14.1
Mean						
1st period	77	137	60	105.2 ± 1.19	12.52 ± 0.84	11.9
2d period	75	132	57	99.6 ± 1.15	12.01 ± 0.81	12.1
3d period	68	134	66	100.3 ± 1.19	12.45 ± 0.84	12.4
All observations						
1st period	67	152	85	105.2 ± 0.77	15.78 ± 0.54	15.0
2d period	67	142	75	99.6 ± 0.70	14.33 ± 0.50	14.3
3d period	40	152	112	100.5 ± 0.77	15.65 ± 0.54	15.6
Diastolic blood pressure						
Lowest						
1st period	22	87	65	53.7 ± 1.43	14.95 ± 1.01	27.8
2d period	12	87	75	49.6 ± 1.29	13.53 ± 0.91	27.3
3d period	20	76	56	52.0 ± 0.96	10.05 ± 0.68	19.3
Highest						
1st period	42	117	75	77.8 ± 1.55	16.22 ± 0.09	20.9
2d period	37	112	65	66.2 ± 1.17	12.26 ± 0.83	18.5
3d period	48	102	54	70.6 ± 1.18	12.4 ± 0.84	17.6
Mean						
1st period	32	97	65	65.5 ± 1.33	13.93 ± 0.94	21.3
2d period	37	77	40	55.5 ± 1.31	13.72 ± 0.93	24.2
3d period	31	82	51	60.8 ± 0.87	9.15 ± 0.62	15.0
All observations						
1st period	22	117	95	65.5 ± 0.88	18.00 ± 0.62	27.4
2d period	12	112	100	55.5 ± 0.72	14.58 ± 0.51	26.3
3d period	20	102	82	61.4 ± 0.62	12.75 ± 0.44	20.8

RESULTS

The mean systolic pressures in each consecutive test period are shown in distribution graphs (chart 1). The diastolic pressures are shown in chart 2. These charts and the table show that the values of the second period of study, i.e., the first repetition of the test procedures, present a downward trend. This is exhibited by the various characteristics of the distribution to a varying degree. The range is a crude statistical datum, but serves to demonstrate the general tendency. In the second period, the range becomes smaller in the majority of cases, chiefly at the expense of the highest values. In the third period, i.e., the second repetition of tests, however, this course

is not so consistent. The systolic ranges increase, owing to a fall in the "minimum" figures, while the diastolic ranges continue to decrease because of the continuous lowering of the "maximum" figures. Too much reliance, of course, cannot be placed on the shifting of the range,

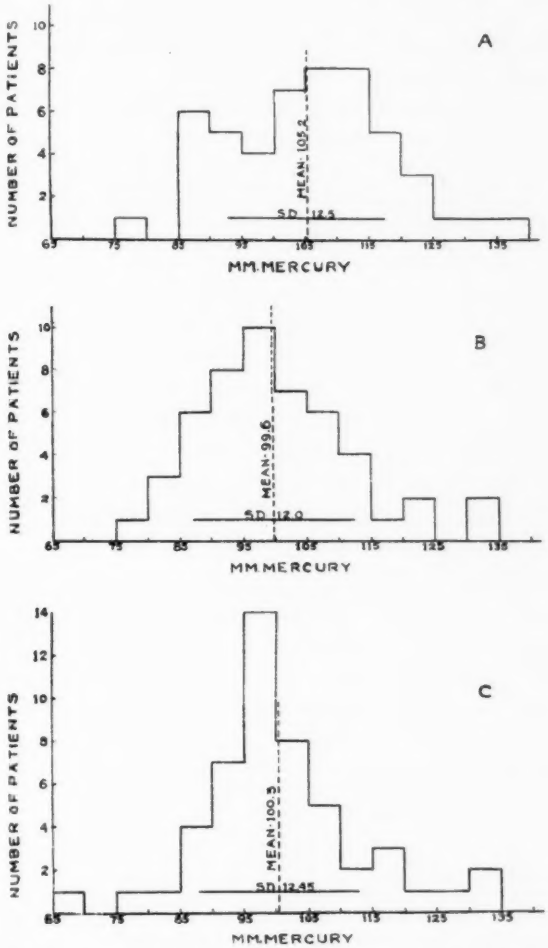

Chart 1.—Frequency distributions of the mean systolic blood pressures of fifty schizophrenic patients in the first, second and third periods (*A*, *B* and *C*, respectively).

partly because it is based on single determinations the number of which, in this group, is not large enough to be conclusive, and partly because such shifts do not necessarily parallel changes in the means. It will be noted that the cases are more compactly grouped in the last two periods.

The column of means (table) reveals this declining trend in the second period even more clearly. Each value diminishes, and the differences are all statistically significant. The mean systolic blood pressure falls from 105 to 99 mm., and the mean diastolic blood pressure from

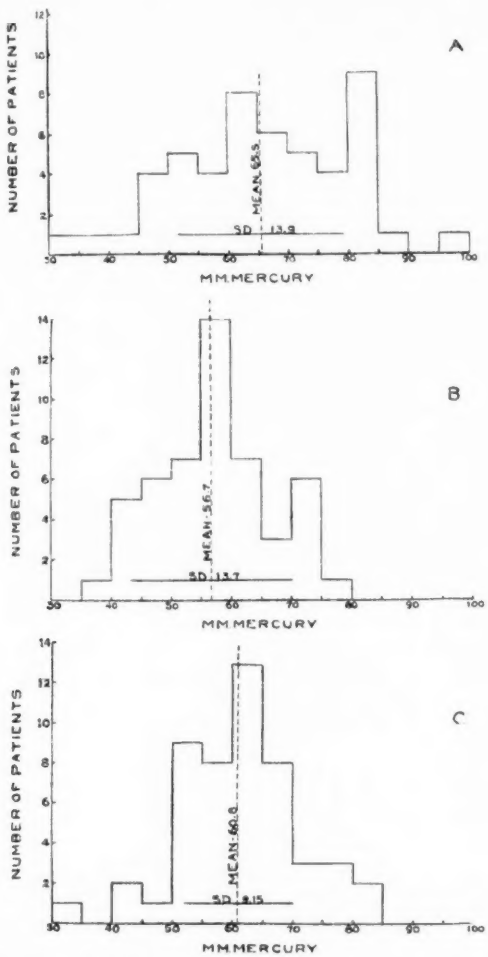

Chart 2.—Frequency distributions of the mean diastolic blood pressures of fifty schizophrenic patients in the first, second and third periods (*A*, *B* and *C*, respectively).

65 to 56 mm. It should be noted that the diastolic readings drop more than the systolic levels. Furthermore, as was noted with the range, the highest measures show a more marked fall than do the lowest. In the third period this tendency is still followed, but not so consistently. The systolic pressures remain at essentially the same levels as they

were in the second period, the "mean systolic" pressure being 100 mm., except for the "highest systolic," which shows a slight rise. On the other hand, the diastolic measurements all increase, but not to the levels of the first period, the "mean diastolic" pressure rising from 55 to 60 mm. Thus, the downward trend, though significant, shows fluctuations in the last period, particularly in the diastolic level.

A study of the standard deviations reveals two interesting facts: (1) The standard deviations of the systolic pressures remain essentially unchanged; (2) the standard deviations of the diastolic pressures show a steady drop in value through the second and third periods. These facts would seem to indicate that the systolic levels are probably all equally reliable since the variation about them remains unchanged, and, on the other hand, that the diastolic reading of the third period, despite its increase, is the least variable and consequently the most reliable. These suppositions are supported by the parallel downward trend of the relative variation in the diastolic blood pressures and the stationary aspect of the corresponding systolic characteristics. The great stability of the last diastolic values is reflected in their smaller variation.

A further point to be considered is the greater variability of the diastolic as compared with the systolic pressures. This phenomenon is evidenced by the much greater coefficients of variation of the former. An estimation of the varying rôles played by differences in technic and of the inherent variability of the diastolic mechanism is difficult to obtain. In an attempt to evaluate this, Freeman, Hoskins and Sleeper [1] found that among four persons simultaneously taking blood pressures, the average error in determining the systolic pressure was 2 mm., and that for the diastolic pressure, 5 mm. Consequently, the personal error in the diastolic determinations is greater than that in the systolic determinations, and as a result too much stress cannot be placed on any factor of greater inherent lability of the processes producing the diastolic pressure.

COMMENT

The analysis has brought forth two facts: (1) The blood pressure, both in its systolic and in its diastolic components, has diminished significantly in the second period and has stayed down in the third period. (2) The highest values have fallen to a greater degree than the lowest values.

This change in pressure was not fortuitous, as the differences are of marked consistency and of definite statistical validity. It is not due to variations in the environmental situation, as this was kept essentially constant. No appreciable difference was found in the nutrition of the patients during these three periods. It is well known that blood pressure, and especially pulse pressure, varies directly with the metabolic

rate.[2] An investigation of the metabolic determinations in the patients under discussion showed no essential differences. Any increase in infections, particularly tuberculosis, which is known to be relatively frequent in schizophrenia, was ruled out by clinical and laboratory investigation. No correlation was found between the blood pressure and the changes in the red blood cell counts; hence, the possible influence of anemia can be eliminated. The mean blood volume, too, was remarkably constant and showed no significant deviations which might account for any change in the vasopressor mechanism.

Another possible cause for the diminution of blood pressure, worthy of some consideration, is the seasonal variation. The first period of study began in August and extended through October; the second ran from November through January; the third ended in the final weeks of April. The mean temperature of the first period is, of course, higher than that of the other two, with the second period being the coldest. The literature on this topic is somewhat scanty. Foster,[3] Cadbury [4] and others have found the blood pressures in tropical or semitropical areas to be lower than those in temperate climates, not only in the natives but in Europeans and Americans living in those regions. Alvarez and Stanley [5] noted, in a study of 6,000 prisoners, that the blood pressures were slightly higher on colder days. Brown's [6] patient with hypertension, whose blood pressure was taken daily for over three years, showed a decrease in the warmer months and an elevation in the colder periods. Griffith, Pucher, Brownell, Klein and Carmer [7] found that the systolic pressure was lowest in the spring. It would seem, therefore, that if seasonal variation were a factor in producing this change in the blood pressure in the series presented, it would have a tendency to raise rather than to lower the pressure.

The sedentary life of the patients as a factor in the production of the hypotension is worthy of brief discussion. The activity of the

2. Read, J. M.: Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, Arch. Int. Med. **34**:553 (Oct.) 1924.

3. Foster, J. H.: Blood Pressure of Foreigners in China, Arch. Int. Med. **40**:38 (July) 1927.

4. Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362 (Sept.) 1922.

5. Alvarez, W. C., and Stanley, L. L.: Blood Pressures in Six Thousand Prisoners and Four Hundred Prison Guards, Arch. Int. Med. **46**:17 (July) 1930.

6. Brown, G. E.: Daily and Monthly Rhythm in the Blood Pressure of a Man with Hypertension: A Three-Year Study, Ann. Int. Med. **3**:1177 (June) 1930.

7. Griffith, F. R., Jr.; Pucher, G. W.; Brownell, K. A.; Klein, J. D., and Carmer, M. D.: Studies in Human Physiology: II. Pulse Rate and Blood Pressure, Am. J. Physiol. **88**:295, 1928.

patients is essentially comparable to that of the medical students whose pressures served as controls and thus cannot have much influence in producing the lower values. Furthermore, as the patients were maintained in a greater state of activity during the period of study than they had been previously and since despite this the tendency of the blood pressure was to fall rather than to rise, the effect of this element is probably of no great importance.

The possibile rôle of emotion in elevating the blood pressure, particularly during the initial examination, demands consideration. The exact estimation of the part played by this process, however, is not so well known and is well worth determining. Previous investigations on the subject of blood pressure have disclosed that this factor must be taken into consideration in evaluating the results of studies of large groups, as well as of individuals. Shepard and Diehl [8] found, in a study of 3,478 university students, that 6 per cent had systolic pressures above 140 mm. of mercury. Repetition of the examination on these students showed readings below this figure in over one-half the cases. Diehl and Sutherland,[9] dealing with a similar though larger group, concluded that when greater precautions were taken to eliminate the influence of excitement, the blood pressures were appreciably lower. With such precautions, 49 per cent of the men who had a systolic pressure of 140 mm. or over on the first examination were found on subsequent trials to have a systolic pressure consistently under 130 mm. The effect of adjustment to the situation or habituation is shown even more clearly in the studies of Diehl and Lees.[10] They took blood pressure readings in 100 healthy college students every five minutes for an hour. It was found that the mean of the first three readings showed significant decreases between consecutive readings, but that after the third reading the blood pressure had stabilized itself so that further changes were too slight to be of importance.

By the elimination of other organic processes, there is left the suggestion of the emotional factor as the possible cause of the lowering of the blood pressure. The greater fall of the highest figures is also in accord with this supposition. It is not to be wondered at that the mental patient, confronted unexpectedly with a series of bewilder-

8. Shepard, W. P., and Diehl, H. S.: Rural and Urban Health, J. A. M. A. **83**:1117 (Oct. 11) 1924.

9. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men: Including a Special Study of Those with Hypertension, Arch. Int. Med. **36**:151 (Aug.) 1925.

10. Diehl, H. S., and Lees, H. D.: The Variability of Blood Pressure: A Study of Systolic Pressure at Five Minute Intervals, Arch. Int. Med. **44**:229 (Aug.) 1929.

ing and at times disagreeable procedures, should show some reaction in the form of an elevation of blood pressure.[11]

Morrison and Diehl,[12] in a neuropsychiatric study of several thousand college students, found that hypertension (on a single reading) was common only in the so-called "neurotic" group. Consequently, the vascular reaction of these even more maladjusted persons is not an unexpected phenomenon. Such a result, it should be noted, is not in accord with the blunting of emotions so commonly described as a feature of this disease. It is, indeed, remarkable that the adjustment to the new environment should have occurred, at least in its physical aspect, so rapidly. Whatever the primary factor may be, however, this review of the data discloses a new level of blood pressure in schizophrenia, one with even more marked differences from the normal than previously recognized, and, in addition, one nearer the true level, if such there be, as it represents a minimizing of the disturbing effect of emotions.

In conclusion, it should be emphasized that one is dealing here with basal blood pressures. In my experience the pressure levels noted during the course of an ordinary routine physical examination are not greatly different in schizophrenic and in nonpsychotic subjects. The essential difference is that in repose the schizophrenic subject shows an unusual "slump." The observations bear out the suggestion of Hoskins,[13] that the psychosis may prove to be characterized by disordered homeostasis. He formulated the working hypothesis that "the homeostasis may be primarily or secondarily organized at displaced (pathologic) levels." The observations herein recorded in one respect explicitly confirm that hypothesis.

SUMMARY

A study was made of the systolic and diastolic blood pressures in 50 cases of schizophrenia in three periods, three months apart. The patients became habituated to daily laboratory procedures.

The systolic and the diastolic pressures were found to be lower in the second than in the first period. The systolic pressure stayed at

11. Since this is a factor impossible of evaluation, I have not considered here the vasomotor reactions of the patient to his own personal problems during the test periods. It is evident that whatever this factor may be, it has not interfered with the general trend.

12. Morrison, A. W., and Diehl, H. S.: Some Studies on Mental Hygiene Needs of Freshman University Students: Preliminary Report, J. A. M. A. **83:** 1666 (Nov. 22) 1924.

13. Hoskins, R. G.: An Analysis of the Schizophrenia Problem from the Standpoint of the Investigator, J. A. M. A. **97:**682 (Sept. 5) 1931.

approximately the lower level in the third period, but the diastolic pressure rose to an intermediate level.

The mean values of the systolic pressures in the three periods were 105.2, 99.6 and 100.3 mm. of mercury, respectively. The diastolic pressures were 65.5, 55.5 and 60.8 mm., respectively.

Season, nutrition, anemia and oxygen consumption rates were excluded as factors causal in the production of the lower pressures. Sedentary life was probably not a significant factor.

The fall in systolic pressure on repeated determinations is ascribed to habituation to the environmental situation.

The observations serve further to emphasize vascular hypotension as a characteristic of the schizophrenic psychosis. The mechanism of its production presents a problem for further research.

FACTORS INFLUENCING EXPERIMENTALLY PRODUCED CONVULSIONS

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In two previous communications the methods of producing convulsions by thujone obtained from wormwood and of controlling them by the administration of acetone bodies, phenobarbital and by dehydration with sugar solutions have been described.[1] Of the various acetone bodies, diacetone alcohol gave the greatest protection against the convulsant drug, the effect being more pronounced than even extreme dehydration. The thujone is emulsified in 6 per cent acacia, and the convulsant dose is from 0.35 to 0.4 cc. of 1 per cent emulsion for each kilogram of body weight. It is important to use rabbits that have not been used before, or those that have not been used for at least a week, and to prevent the animal from struggling, as this will decrease its susceptibility to convulsions due to thujone.

Wilder's original hypothesis attributed the effect of ketogenic diet on epileptic convulsions to the sedative effect of the aceto-acetic acid. The following experiments were carried out with this substance. As is well known, it is very unstable. A 5 per cent solution of aceto-acetic acid and another of sodium aceto-acetate were kept on ice and used immediately. Each of six healthy rabbits was given intravenously an amount of the solution equal to 0.1 Gm. aceto-acetic acid for each kilogram of body weight. This was followed in seven minutes by a single convulsing dose of thujone. As may be noted in table 1, only one of the six rabbits responded with a convulsion. The experiment was then repeated on six other rabbits, 0.1 Gm. of sodium aceto-acetate for each kilogram of body weight being used. In this case not one of the animals had a convulsion. To compare this effect with that of diacetone alcohol, the experiment was repeated a second time, an equal amount of diacetone alcohol being used. The diacetone alcohol did not

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From the Section on Pediatrics, the Mayo Clinic.

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1. Keith, H. M.: Influence of Various Factors on Experimentally Produced Convulsions, Am. J. Dis. Child. **41**:532 (March) 1931. Keith, H. M.: Further Studies on the Control of Experimentally Produced Convulsions, J. Pharmacol. & Exper. Therap. **44**:449 (April) 1932.

have so pronounced an effect as the aceto-acetic acid or the sodium aceto-acetate until the amount of the alcohol was increased to 0.5 Gm. for each kilogram of body weight. The experiment was also carried out with an equal amount of ethyl aceto-acetate in 5 per cent solution. This had less anticonvulsive effect than the diacetone alcohol and much less than the sodium aceto-acetate. It may be noted that the molecular weight of sodium aceto-acetate is 124 and that of the ethyl ester, 130.

Diacetone Alcohol and Phenobarbital.—It was previously found that if both drugs were given by stomach tube, phenobarbital in amounts of 0.025 Gm. for each kilogram of body weight had about the same anticonvulsive effect as 0.5 Gm. for each kilogram of diacetone alcohol. The experiment was repeated, both drugs being given intravenously.

TABLE 1.—*Rabbits Given Various Substances Intravenously to Prevent the Convulsions Due to Thujone* *

Substance	Dosage, Gm. per Kg.	Animals Used	With Convulsions	Without Convulsions	
				Number	Per Cent
Aceto-acetic acid	0.1	6	1	5	83.0
Sodium aceto-acetate	0.1	6	0	6	100.0
Diacetone	0.1	6	3	3	50.0
Alcohol	0.5	8	1	7	87.5
Ethyl aceto-acetate	0.1	6	4	2	33.3
Sodium phenobarbital	0.025	6	2	4	66.6
Acetic acid	0.25	6	3	3	50.0
Lactic acid	0.1	8	4	4	50.0
Citric acid	0.1	10	4	6	60.0
Hydrochloric acid	0.1	12	5	7	58.0
Sodium citrate	0.1	10	5	5	50.0
Sodium pyruvate	0.2	5	1	4	80.0

* The interval between injection of the drug and administration of thujone was from five to seven minutes.

In this instance the action of the diacetone alcohol was a little more marked than that of phenobarbital within five minutes, but both drugs prevented convulsions forty minutes after their injection.

Effect of Acids.—It has been suggested that acid as such tends to prevent convulsions. Elsberg and Stookey,[2] and Lennox, Nelson and Beetham [3] injected lactic acid into the blood stream of animals and noted that their susceptibility to convulsions was somewhat lessened. Pike [4] and his associates recently stated that lactic acid given intravenously

2. Elsberg, C. A., and Stookey, B. P.: Studies on Epilepsy: I. Convulsions Experimentally Produced in Animals Compared with Convulsive States in Man, Arch. Neurol. & Psychiat. **9**:613 (May) 1923.

3. Lennox, W. G.; Nelson, Roger, and Beetham, W. P.: Studies in Epilepsy: VI. Factors Affecting Convulsions Induced in Rabbits, Arch. Neurol. & Psychiat. **21**:625 (March) 1929.

4. Pike, F. H.; Osnato, M., and Notkin, J.: The Combined Action of Some Convulsant Agents in Small Doses and the Action of Bromides on Experimentally Produced Convulsions, Arch. Neurol. & Psychiat. **25**:1306 (June) 1931.

enhanced the convulsive action of absinth. Acetic, lactic, citric and hydrochloric acids were given intravenously in 5 per cent solution and in amounts of 0.1 Gm. for each kilogram of body weight. Pyruvic acid, a keto-acid, was given in the form of sodium pyruvate, and sodium citrate was also tested. All of the acids caused some irritation on injection, the action of citric acid being the most pronounced. In each case there was a definite anticonvulsive effect, although in the case of acetic acid the amount given had to be increased to 0.25 Gm. for each kilogram of body weight. Citric acid and sodium citrate corrresponded closely in their anticonvulsive action. Sodium pyruvate was also definitely anticonvulsive, but here again the amount had to be increased to 0.2 Gm. for each kilogram of body weight to obtain a comparable effect.

Fröhlich and Solé,[5] in experiments on frogs, found that alkali increased the action of alkaloid convulsants but had no effect on the action of picrotoxin. In my experiments, sodium bicarbonate did not increase the rabbits' susceptibility to convulsions. Indeed, in doses of 0.3 Gm. for each kilogram of body weight, it had an anticonvulsive effect.

Epinephrine, Solution of Pituitary, Ephedrine and Similar Drugs.—To note the effect of epinephrine, 0.1 cc. of 1:1,000 solution of epinephrine hydrochloride was injected with the normal convulsing dose of thujone. The succeeding convulsion was much more severe than usual, the animal becoming prostrated and apparently unconscious. This increase in the severity of the convulsions when epinephrine was combined with absinth was also noted recently by Notkin and Pike.[6] The experiment was repeated on other animals with half the convulsant dose of thujone. Again the animals had convulsions, this time of moderate severity. A third group was given epinephrine and one quarter of the convulsant dose of thujone, but none of the animals responded with an attack.

The experiments were then repeated, pituitary, pitressin and ephedrine being used. It may be noted in table 2 that both the pituitary preparations acted as did the epinephrine, but the ephedrine did not. Since the ability to elevate the blood pressure is common to epinephrine, pituitary and pitressin, I tried to reduce the animals' susceptibility to convulsions by using substances to reduce blood pressure, for example, sodium nitrite and crotalin. Sodium nitrite, although used in large

5. Fröhlich, A., and Solé, A.: Der Einfluss von Säuren und Alkalien auf die Wirkung einiger Krampfgifte, Arch. f. exper. Path. u. Pharmakol. **104**:32, 1924.

6. Notkin, J., and Pike, F. H.: Some Experiments on the Effects of Caffeine, Adrenalin, and Bromides upon the Susceptibility of Experimentally Induced Convulsions in Animals, Am. J. Psychiat. **10**:771 (March) 1931.

amounts, did not alter the susceptibility, and crotalin, which gives an even greater reduction in blood pressure, influenced it little, if any. It may be noted here that ephedrine raises the blood pressure much less than epinephrine, but only slightly less than pitressin. Why the two latter substances should augment the convulsive effect of thujone and the ephedrine fail to do so is not clear.

It is a fact well known in pharmacology that animals given a powerful drug become refractory to that drug for varying periods of time. This has been observed repeatedly in rabbits given thujone, the refractory period being as long as three days. This tolerance can be eliminated entirely by epinephrine, and the convulsion can invariably be repeated

TABLE 2.—*Rabbits Given Various Substances Intravenously to Observe the Effect on Convulsions Due to Thujone*

Substance	Dosage	Animals Used	Convulsive Dose of Thujone	With Convulsions	Without Convulsions	With Convulsions; per Cent	Comment
Epinephrine 1:1000...	0.1 cc.	5	1	5	0	100.0	Severe prostration
Epinephrine 1:1000...	0.1 cc.	9	½	9	0	100.0	
Epinephrine 1:1000...	0.1 cc.	5	¼	0	5	0.0	
Controls.....	.....	16	..	3	13	18.7	
Pituitary.....	0.5 cc.	6	½	5*	1	83.0	
Pitressin.....	0.1 cc.	7	½	7	0	100.0	
Ephedrine sulphate..	0.01 Gm.	8	½	2	6	25.0	Slight attacks
Crotalin.....	0.0001 to 0.0009 Gm. per Kg.	9	1	7	2	77.0	
Sodium nitrite.....	0.1 to 0.2 Gm. per Kg.	4	1	4	0	100.0	Animals died in half hour
Desiccated thyroid...	230 Gm. daily for 18 days	4	½	0	4	0.0	
Thyroxine.....	0.001 Gm. per Kg. on 2 successive days	6	½	2	4	33.3	
Insulin.....	3 units	6	½	1?	5	20.0	

* Convulsions were delayed about a minute.

either within a very few minutes or after many hours by the addition of a small amount of epinephrine to the thujone emulsion.

To determine how long the effect of epinephrine and pitressin would last in augmenting the susceptibility to convulsions, each of fifteen rabbits was given 0.1 cc. epinephrine and fifteen 0.1 cc. pitressin intravenously. At intervals of from two to ten minutes, different animals were given half of a convulsant dose of thujone each. As may be seen in table 3, both drugs were active during a similar period, that is, for at least three minutes.

Four rabbits were given 230 mg. of desiccated thyroid gland daily for a period of two and a half weeks. Six were given thyroxine intravenously on two successive days in amounts of 1 mg. for each kilogram of body weight. All the rabbits received half the normal convulsant dose of thujone. Two of these animals had mild attacks; the remaining six did not. Although there was no striking evidence of increase in the

susceptibility to convulsions, as I had anticipated, evidence in favor of the opposite result is not in agreement with the statement of Uyematsu and Cobb.[7]

In view of the fact that hypoglycemia can induce convulsions, each of six rabbits was given 3 units of insulin, followed in two hours by half of a convulsant dose of thujone. One of the animals had a very slight attack.

McQuarrie,[8] in 1929, demonstrated that the administration of the antidiuretic hormone of the pituitary gland favored the occurrence of seizures in cases of epilepsy, whether water was given in large amounts or was restricted. This effect did not occur immediately (as in the experiments mentioned) but after a series of injections of the hormone,

TABLE 3.—*Rabbits Given Epinephrine and Pitressin Intravenously Followed at Different Intervals by One-Half Convulsing Dose of Thujone*

Substance	Animals Used	Interval Minutes	With Convulsions	Without Convulsions	With Convulsions, per Cent	Brain Solids, per Cent	
						Range	Average
Epinephrine 0.1 cc. 1:1000	6	2–3	5	1	83.3		
	6	4–5	1	5	16.7		
	3	10	0	3	0.0		
Pitressin 0.1 cc	6	3	5	1	83.3		
	6	5	1	5	16.7		
	3	8	0	3	0.0		
Pitressin 0.5 cc. + 10 to 15 per cent of body weight of water	12	120	4	8	33.3	21.8 to 18.7	20.21 ± 0.20
Water alone, 10 per cent of body weight	3	...	0	3	0.0	21.4 to 19.8	
Controls	31	...	..	..	....	23.3 to 20.7	21.88 ± 0.80
Difference							1.67* ± 0.21

* This is a real difference and is not due to sampling.

and it was suggested that hydration of the tissues as a result of the injection of hormone was responsible for the effect. A number of rabbits were given 0.5 cc. of pitressin intramuscularly, and during the ensuing one and a half hours water in amounts of from 10 to 15 per cent of the body weight was given by stomach tube, following the method of Greene and Rowntree.[9] At the end of two hours each rabbit was

7. Uyematsu, Schichi, and Cobb, Stanley: Preliminary Report on Experimental Convulsions: Convulsions Produced by Administration of Chemical Substances, Arch. Neurol. & Psychiat. **7**:660 (May) 1922.

8. McQuarrie, Irvine: Epilepsy in Children: The Relationship of Water Balance to the Occurrence of Seizures, Am. J. Dis. Child. **38**:451 (Sept.) 1929.

9. Greene, C. H., and Rowntree, L. G.: The Effect of the Administration of Excessive Amounts of Water on Body Temperature, Am. J. Physiol. **80**:230 (March) 1927.

given half of a convulsive dose of thujone; the animals were then killed, and the water content of the brain was determined. The rabbits were possibly a little more susceptible than normal rabbits to the thujone, and the water in the tissues of the brain was definitely increased. In the control animals, given water only, the water content of the brain was perhaps slightly increased, although less than in the animals that were given water and pitressin.

COMMENT

In a previous paper it was found that of several acetone bodies tested, diacetone alcohol had the most pronounced anticonvulsive effect. In the present study I have been able to compare its action with that of aceto-acetic acid and its sodium salt. It can readily be seen that the two last are much more effective, requiring only one fifth as much to give the same anticonvulsive action (0.1 Gm. for each kilogram of body weight). On the other hand, a still smaller amount of phenobarbital (0.025 Gm. for each kilogram of body weight) gives a comparable effect, although it is a little slower in action.

The anticonvulsive effect of the various acids is also of interest. In each experiment the acid apparently prevented convulsions in about 50 per cent of the animals. Pike, Osnato and Notkin have recently used lactic acid to produce convulsions in cats, and they stated that lactic acid enhances the convulsant action of absinth. The concentration of the solution of lactic acid which they used is not given. Their findings do not agree with the results in the foregoing experiments nor in those of Elsberg and Stookey, or Fröhlich and Solé. The former used amounts of lactic acid similar to the "convulsing doses" of Pike and his associates, namely, 1 Gm. for each pound (500 Gm.) of body weight of animal. Fröhlich and Solé perfused frogs with 1 : 500 and 1 : 1,000 solution. I have used 0.1 Gm. for each kilogram of body weight in 5 per cent solution. No twitching or jerking was noted, although respiration was accelerated. None of the five acids injected caused convulsions, although acetic acid was given in amounts up to 0.25 Gm. for each kilogram of body weight. The anticonvulsive action of 0.3 Gm. for each kilogram of body weight of sodium bicarbonate is worthy of note, even if it is not marked. Why this should have the same action as the injection of acid is not clear.

Of the various acids used, aceto-acetic had the most pronounced effect, pyruvic acid was somewhat less active. The formulas of these acids are as follows: pyruvic acid, $CH_3COCOOH$; aceto-acetic acid, CH_3COCH_2COOH; diacetone alcohol, $(CH_3)_2COHCH_2COCH_3$, which is also anticonvulsive. All these substances contain the CH_3CO grouping, whereas diacetone alcohol and aceto-acetic acid contain the CH_3COCH_2 group.

The action of epinephrine and solution of pituitary in contradistinction to ephedrine is difficult to explain. Epinephrine has a much more pronounced action on the blood pressure than ephedrine, and it was thought at first that this was the significant factor. Pitressin, however, was found to cause elevation of blood pressure similar in extent to that of ephedrine; yet the former markedly increased the convulsant action of thujone and the latter did not. Also, the two drugs causing a drop in blood pressure had no definite anticonvulsive effect. This difference in action of epinephrine, pitressin and ephedrine needs further investigation.

Of the remaining factors, the elevation of basal metabolism by the administration of desiccated thyroid gland and thyroxine did not increase the rabbits' susceptibility to convulsions comparable to the effect of epinephrine and pituitary preparations, nor did the use of insulin. This susceptibility was perhaps slightly increased by the administration of large amounts of water by stomach tube, preceded by the intramuscular injection of pitressin, and there was a slight increase in the water content of the tissues of the brain in the latter group.

CONCLUSIONS

1. Of the various acetone bodies tested, aceto-acetic acid and its sodium salt have the most pronounced effect in preventing thujone convulsions.

2. The injection of acids (acetic, lactic, citric and hydrochloric) as such and of sodium pyruvate has a definite anticonvulsant effect under the conditions of the experiment, but they are less effective than aceto-acetic acid.

3. Epinephrine, pituitrin *S* and pitressin greatly augment the convulsant action of thujone and the action of epinephrine, and pitressin persists for at least three minutes after intravenous injection. These drugs will cause a subconvulsant dose to become convulsant.

4. Epinephrine eliminates the refractory period due to the administration of thujone.

5. The administration of desiccated thyroid gland and thyroxine did not definitely increase the susceptibility of the rabbits to convulsions produced by thujone.

6. The administration of insulin to rabbits with resulting hypoglycemia did not increase their susceptibility to convulsions.

7. Large amounts of water by stomach tube either alone or accompanied by intramuscular injection of pitressin may possibly increase the animals' susceptibility to convulsions produced by thujone. There was a slight increase in the amount of water in the tissues of the brain of animals receiving pitressin.

CHOLESTEROL AND LECITHIN CONTENT OF THE BLOOD IN CRYPTOGENIC EPILEPSY

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The etiology of many types of epilepsy is still unsolved. The term "cryptogenic" as used in this article defines cases in which there is no definite pathologic condition.[1] It may well be that some of the manifestations of this disease are of metabolic origin; therefore, an accumulation of biochemical data is of the utmost importance. Thus far few observations on cholesterol have been published. Perhaps the most comprehensive investigations are those carried out by Robinson, Brain and Kay [2] and by Osnato and his co-workers.[3] Although their findings are interesting, we considered further work necessary.

This report presents observations on the occurrence of cholesterol and lecithin in the blood in forty-seven cases of epilepsy and in the spinal fluid in twenty cases. The patients were all inmates of the Manhattan State Hospital. The blood was drawn in the morning before breakfast. Cholesterol was determined according to the Myers and Wardell technic [4] and lecithin by the Krasnow and Rosen method.[5]

The details are listed in the accompanying table. As may be seen, the cholesterol content of whole blood varies from 130 to 250 mg. per hundred cubic centimeters, with an average of 177 ± 28. The lecithin content ranges from 172 to 302 mg. per hundred cubic centimeters of

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From the Department of Dermatology and Syphilology of the New York Post-Graduate Medical School and Hospital and the Manhattan State Hospital.

1. Notkin, J.: Encephalographic Studies in Cryptogenic Epilepsy, Arch. Neurol. & Psychiat. **26**:115 (July) 1931.

2. Robinson, S. H. G.; Brain, W. R., and Kay, H. D.: Lancet **2**:325, 1927.

3. Osnato, M.; Killian, J. A.; Garcia, T., and Mattice, M. R.: Brain **50**:581, 1927.

4. Krasnow, F., and Rosen, A. S.: J. Lab. & Clin. Med. **14**:967, 1929.

5. Krasnow, F., and Rosen, A. S.: Proc. Soc. Exper. Biol. & Med. **26**:67, 1928; Lecithin and Cholesterol Studies in Dermatophytosis, Arch. Dermat. & Syph. **23**:132 (Jan.) 1931; Cholesterol Studies in Syphilis, ibid. **20**:75 (July) 1929.

whole blood, the average being 242 ± 27. These average values show little divergence from the figures for ninety-nine clinically normal persons. Analyses in twenty-seven normal persons showed: 171 ± 16 for cholesterol and 242 ± 22 for lecithin. The distribution, however, is different; in 21 per cent of the cases of epilepsy the cholesterol contents

Cholesterol and Lecithin Content of Whole Blood in Epilepsy: Forty-Seven Cases

Serial Number	Age	Onset of Convulsion. Age	Cholesterol, Mg. per 100 Cc. Whole Blood	Lecithin, Mg. per 100 Cc. Whole Blood	Days After Last Convulsion	Days Before Succeeding Convulsion
6	25	16 years	149	225	121	35
10	37	3 years	147	230	7	15
22	44	32 years	157	217	14	9
16	47	26 years	207	237	2	1
4	38	8 years	166	237	22	8
3	55	25 years	170	255	13	1
2	46	34 years	230	270	13	6
1	31	8 months	170	245	0	2
24	33	25 years	143	223	19 ?	0
15	54	25 years	180	245	20	12
14	26	8 years	164	230	1	22
12	32	?	158	202	11	1
19	21	15 years	130	217	1	3
13	27	13 years	133	191	1	2
18	55	25 years	137	217	1	4
17	34	?	158	202	2	1
23	37	9 years	184	202	0	7
21	40	18 years	250	235	6	7
20	63	Infancy	161	172	17	30
11	50	33 years	196	270	5	3
9	25	10 years	143	225	4	1
8	43	35 years	162	242	Several years	0
27	40	23 years	193	250	50	95
7	24	16 years	140	182	..	153
5	37	20 years	151	220	180	0
25	40	25 years	187	265	2	0
26	41	27 years	170	260	108	6
1	25	16 years	168	250		
2	55	50 years	199	250		
3	40	23 years	213	275		
4	40	18 years	230	275		
5	54	18 years	147	242		
6	50	25 years	205	262		
7	44	7 years	166	225		
8	63	Infancy	213	272		
9	48	32 years	193	250		
10	39	8 months	174	260		
11	50	33 years	205	302		
12	32	.....	158	300		
13	40	35 years	169	265		
14	55	25 years	168	237		
15	40	26 years	172	260		
16	34	13 years	200	277		
17	44	7 years	203	252		
18	44	32 years	176	247		
19	73	10 years	210	270		
20	54	25 years	218	247		

fall below 171 — 16 mg. and 34 per cent are above 171 + 16 mg. per hundred cubic centimeters of whole blood, whereas the figures for our normal group are respectively 16 and 16, with 68 per cent within 171 ± 16. For lecithin, the values for 19 per cent fall below 242 — 22 mg. and those for 23 per cent above 242 + 22 mg. per hundred cubic centimeters of whole blood, leaving 57 per cent in the range of 242 ± 22, corresponding to 7, 14 and 78 per cent for the normal group.

These studies on blood were supplemented with analyses of spinal fluid. Thus far all attempts to find lecithin have been unsuccessful. Very small amounts of cholesterol were found in all spinal fluid examined. The technic for the determination for cholesterol was that used in the blood.[4] However, it was first necessary to concentrate the spinal fluid by evaporating 10 cc. to 1 cc.

CONCLUSIONS

1. The average values for the cholesterol and lecithin content of the blood in cryptogenic epilepsy do not differ from the normal. However, the percentage of patients giving values above and below 171 ± 16 mg. for cholesterol and 242 ± 22 mg. for lecithin is greater than in the corresponding percentage for the normal group.

2. All specimens of spinal fluid examined contained small amounts of cholesterol.

3. No correlation is apparent between the cholesterol content of the spinal fluid and that of the blood.

INCUBATION PERIOD OF CLINICAL NEUROSYPHILIS

H. HANFORD HOPKINS, M.D.
BALTIMORE

Since the definite establishment of syphilis as the cause of tabes and dementia paralytica, considerable speculation has arisen and not a few pertinent facts have been obtained concerning the effect of the treatment of early syphilis on the pathogenesis of these two late manifestations. It has been asserted by many neurologists that any treatment of early syphilis, and particularly treatment with arsphenamine, predisposes the syphilitic patient to the development of parenchymatous neurosyphilis,[1] a concept which has not been substantiated in its entirety by later investigations.[2] Coincidentally, it has been reported by many observers that the symptoms of tabes and dementia paralytica are now appearing at shorter and shorter intervals after the date of infection. The period between infection and the outbreak of *symptoms* of neurosyphilis has been aptly called, by Ravaut, the incubation period of neurosyphilis. It is in this sense that the term "incubation period" is used throughout this paper. A number of German and French syphilologists have shown that the incubation period of tabes and dementia paralytica is markedly influenced by treatment for early syphilis, and that such treatment, whether consisting of the administration of preparations of mercury or arsphenamine, tends to shorten the incubation period.[3]

I present evidence to show that not only is the incubation period of tabes and dementia paralytica shortened if treatment is given during the period of early syphilis, but also that inadequate treatment given at any

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From the Syphilis Division of the Medical Clinic, Johns Hopkins Hospital.

This study has been supported by a grant from the Committee on Research in Syphilis, Inc.

1. Willmans, K., and Steiner, G.: Syphilis und Metasyphilis, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:875, 1925.

2. Smith, J. C.: Notes on the Appearance of Dementia Paralytica and the Relation Between Its Frequency and the Antisyphilitic Treatment, Acta psychiat. et neurol. **1**:346, 1926. Frankl, S.: Der Einfluss therapeutischer Massnahmen auf das Auftreten von Tabes und Paralyse, München. med. Wchnschr. **77**:1879, 1930.

3. Williams.[1] Jagdhold, H.: Ueber die Beziehungen der specifischen antiluetischen Behandlung zum Entstehen der Metalues, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:151, 1930. Sezary, A., and Roudinesco: L'incubation du tabes et de la paralysie générale, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:968, 1931.

time during the course of syphilis is apt to shorten the interval before the onset of neurologic symptoms; furthermore, that the incubation period of clinical neurosyphilis in general may be affected in the same manner.

The material for this study was taken from 1,200 patients who at the time of their admission to the syphilis clinic of the Johns Hopkins Hospital had neurosyphilis, or in whom it subsequently developed. Approximately one half of these patients gave a history of early syphilis and were available for an estimate of the incubation period. The remainder are necessarily excluded. From those with a history of early manifestations of syphilis, patients with neurorecurrence or early syphilitic meningitis were also excluded, because in them the incubation period is measurable in weeks or months rather than in years. There

The Effect of Treatment on the Incubation Period of Tabes, Dementia Paralytica and the Tabetic Form of Dementia Paralytica, and of Meningovascular Syphilis

	Number of Cases	Mean Incubation Period
Tabes		
Untreated	71	24.02 ± 0.68 years
Treated	68	14.64 ± 0.48 years
Dementia paralytica and the tabetic form of dementia paralytica		
Untreated	52	19.54 ± 0.56 years
Treated	65	15.32 ± 0.58 years
Unclassified (meningovascular) syphilis of the central nervous system		
Untreated	165	13.94 ± 0.38 years
Treated	83	10.48 ± 0.6 years

remained for analysis 139 cases of tabes, 117 of dementia paralytica and the tabetic form of dementia paralytica and 248 of all other types of neurosyphilis. Each group was divided into two further subgroups: (1) patients having had no antisyphilitic treatment prior to the appearance of symptoms of neurosyphilis and (2) patients having had previous antisyphilitic treatment with mercury or arsenic or both. The type of treatment given in the latter group varied from what might be called excellent, i. e., more than one year of continuous weekly treatment consisting of courses of arsphenamine alternating with courses of mercury or bismuth, to very inadequate treatment, consisting of a few injections of arsphenamine or a few mercury rubs. About one fourth of the group had received approximately a year of treatment at some time prior to the development of symptoms of neurosyphilis. In about one half of the group treatment was begun during the early manifestations of the disease; in the other half it was begun later in the course

of the infection; in not a few of the latter it was begun just before the development of neuraxis symptoms.

The effect of treatment on the incubation period may be seen in the accompanying table. In each group a shortening of the incubation period is noted in the treated patients, this being particularly marked in the patients with tabes. The untreated patients with tabes had a mean incubation period of 24.02±0.68 years; the previously treated group, 14.64±0.48 years. For the patients with dementia paralytica and the tabetic form of dementia paralytica the figures are 19.54±0.56 years, and 15.32±0.58 years; for the unclassified group of neurosyphilitic patients, 13.94±0.38 years and 10.48±0.6 years. In each group the difference between treated and untreated groups is statistically highly significant, the difference being at least more than four times the probable error of the difference.

A possible explanation of the foregoing observation is that the treatment of patients with potential or even actual late neurosyphilis is capable of affecting adversely the resistant state built up by the patient in much the same way that inadequate treatment during the early stages of syphilis is believed to interfere with the resistance-building mechanism by predisposing the patient to the development of a neurorecurrence. Another possible explanation is that antisyphilitic drugs themselves exert some deleterious action on the nerve tissue which permits the progression of an infection with Spirochaeta pallida, already present in the tissues of the nervous system. The observations cited do not assist in determining which of these explanations is correct, but the former seems more probable.

One is forced to the conclusion, however, that inadequate treatment of a patient with late neurosyphilis (using the term late neurosyphilis, it must be remembered, to designate invasion of the central nervous system, with or without clinical signs of involvement, but without definite symptoms) may be productive of consequences in the central nervous system potentially as serious as inadequate treatment of early syphilis. Emphasis is laid on the fact that although inadequate treatment of late syphilis does not increase the incidence of neurosyphilis in the group of patients in whom clinical neurosyphilis is ordinarily destined to develop, inadequate treatment may be followed by the earlier appearance of clinical symptoms of involvement of the neuraxis. Neither should this statement be construed to mean that treatment of late nonsymptomatic neurosyphilis is contraindicated, since I have elsewhere presented evidence [4] that proper treatment will prevent the development of clinical neurosyphilis.

4. Moore, J. E., and Hopkins, H. H.: Prognosis of Early and Late Asymptomatic Neurosyphilis, J. A. M. A. **95**:1637 (Nov. 29) 1930.

CONCLUSIONS

1. From a survey of the more recent literature, it is not apparent that modern treatment of early syphilis has increased the incidence of tabes and dementia paralytica.

2. The inadequate treatment of early or late syphilis shortens the incubation period, not only of tabes and dementia paralytica, but also of late meningovascular neurosyphilis.

Clinical Notes

THE BRAIN IN A CASE OF MOTOR APHASIA IN WHICH IMPROVEMENT OCCURRED WITH TRAINING

H. Douglas Singer, M.D., F.R.C.P. (London), and A. A. Low, M.D., Chicago

The principal reason for reporting this case is the remarkable improvement that followed persistent training in spite of the fact that an autopsy, performed twenty-five years later, revealed complete absence of the hinder parts of the second and third frontal convolutions.

REPORT OF CASE

Clinical History.—Mrs. S. was born in England in 1865. There was nothing of significance in the family or early history of the patient. She was always well. She took some training as a nurse and supported herself and assisted her husband to complete a college course by doing practical nursing. The only fact of significance in the history prior to the stroke was that in 1902, after having worked very hard and having assumed much responsibility in the care of a patient, she had what was described as a "spell." During the attack, she "lost her speech" for two or three days and then recovered completely. Subsequent to this, in September, 1902, she had a miscarriage which was without untoward results.

On March 23, 1904, at the age of 39, the patient gave birth to a healthy child after an uneventful pregnancy. Labor was difficult and prolonged, lasting thirty-six hours, and delivery was completed with forceps. Following this, the patient was extremely exhausted. On March 24, while using a bed pan, she suddenly became unconscious and fell over to the right. She remained in coma for twenty-four hours, and after this was clouded and unable to talk; the right side of the body—the face, arm and leg—was completely paralyzed. After a few days she seemed to understand what was said to her, but the only sounds she was able to utter were "o-de-dar." These sounds were repeated in every effort to speak. The general condition continued to improve, and the patient became able to make herself understood to some extent by signs. There was no improvement, however, in speech or in the ability to move the arm or the leg during the next two years.

Course.—In the spring of 1906, one of us (Dr. Singer) saw her in a nursing home. She then presented a severe hemiplegia, with no movement in the hand and marked contracture; the leg could be moved, but there had been no effort to walk. She was alert and excitable. She evidently understood everything that was said to her; she recognized objects and their uses, employing her left hand. She was unable to write with the left hand and could read nothing. Her only verbal responses were the rapidly uttered and frequently repeated "o-de-dar." She showed considerable irritability concerning her inability to respond.

Read by title at the Fifty-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June, 1932.

When the suggestion was made to the patient that it might be possible to teach her to talk again and certainly to be able to walk, she shook her head vigorously in denial and made gestures that suggested that she was entirely hopeless. Persuasion had to be used to induce her to make attempts.

After some persuasion, on being told how to place her lips and to make a blowing effort and then to combine this with the "e" sound of her "o-de-dar," she finally at this sitting succeeded in pronouncing the sound "bee." The "b" was chosen because of its similarity and yet difference from the "d" that she used spontaneously. Following this first success, she was able to produce the "b" on request and at once became fully cooperative. The "b" was then practiced in conjunction with the vowel sounds "o" and "ar," both of which she used in her spontaneous utterance.

Subsequent training was carried out, under direction, by the husband, a man of unusual intelligence and devotion. With daily practice, she was taught to utter all the consonants with the exception of "q" and "kl." These were never acquired; she always pronounced "kl" as "kr." Each consonant was then practiced in combination with the various vowel sounds.

The next step, after from six to eight weeks, was the addition of terminal consonants in the production of monosyllabic words, each word being associated with the object thus named: bed, bowl, book, pin, cup, etc. From monosyllabic words, the next progress was to bisyllabic names, which were always associated with the corresponding objects: table, window, towel, napkin, etc.

During the same period, she was encouraged to use the right leg, and she soon developed the power to walk with assistance. By August, 1906, when she returned to visit with relatives in England, she was able to use a large number of words with some freedom and to walk with the aid of a crutch. The training was continued with the same assiduity in England, where she remained until 1914, when she returned to the United States. She was not seen again by us subsequent to August, 1906, so that the report of her progress has been secured only through the husband.

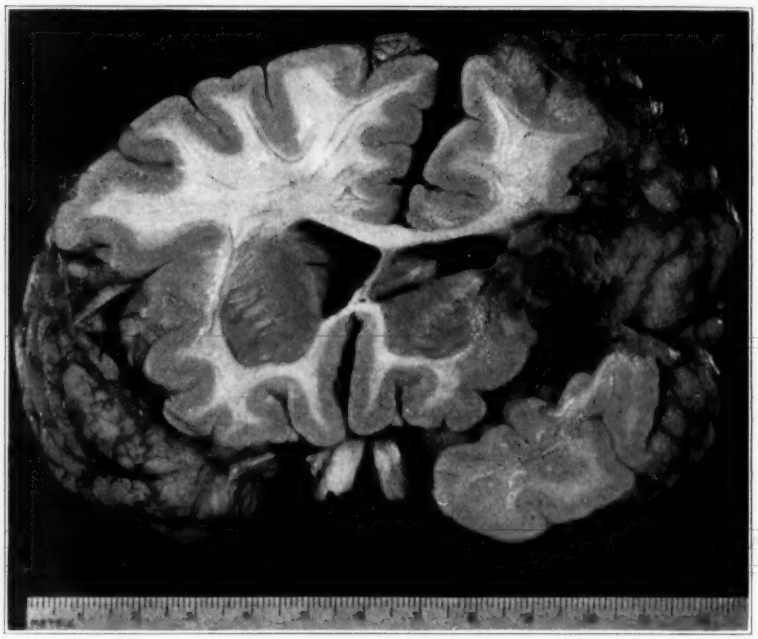
In 1914, on her return from England, she was able to walk with a cane, but had no use of the right hand. However, she used the hand much like a false limb to help her in many duties. At this time she assumed charge of the home with her husband and daughter. She dressed herself without aid, except that she could not do her hair. She was an excellent cook and, without assistance, would prepare meals for several guests as well as for the immediate family. She supervised her daughter's education and talked with her about her work even through high school and college. She took much interest in church affairs and organized her house work with great precision.

With regard to speech, she was said to have a vocabulary of fully five hundred words, which she used freely and always intelligibly to those who knew her well. Strangers had some difficulty in understanding her at times, but for the most part she talked distinctly.

There was little or no return of the ability to read, but some striking facts are described. It is said that she appeared to follow the progress of the World War through pictures and headlines in the paper, but she could not read a paragraph. She liked to be read to, her favorite books being the simple Scotch stories of Annie Swan. After hearing them she would pore over the pages and could pick out correctly the names of the characters. She had difficulty in grasping abstract passages when read to her. For example, she could not grasp the works of George Eliot. She followed the action of the story, but failed to grasp the more abstract commentaries.

She learned to write a little with the left hand, and was in the habit of making out the grocery lists. In doing this, however, she seemed to be unable to write down the articles unless she had the printed words in front of her, even though she could say the name of the article. She was accustomed to use a cook book, over which she pored a great deal, to help in making out her lists, and she seemed to know where to find the articles she wanted; when she saw the word "potatoes," for instance, in print she could write it out in script. She was unable to write spontaneously or to dictation without such aid.

For two or three years before death she became more feeble and was unable to walk around, but her mind was as clear as at any time. She died on Nov. 7, 1929, from pneumonia. Permission for a postmortem examination of the brain alone was



The brain in the case reported.

offered spontaneously, after no word had been received of the patient for many years.

Observations at Necropsy.—Gross Examination: On frontal section, a large cavity was revealed in the left side, involving the second and third frontal convolutions. The cavity involved the cortex and extended down to the corpus striatum and the wall of the left lateral ventricle. The floor of the cavity was covered with a number of blood vessels. The subjacent temporal lobe was intact. The mesial wall of the cavity was formed by the lateral ventricle and the corpus striatum; the upper wall, by the first frontal convolution; the floor was the temporal lobe. The ventricles were moderately dilated; the blood vessels were markedly sclerosed.

Microscopic Examination: Sections from the first, second and third frontal convolutions, and from the occipital lobe, corpus striatum, optic thalamus, substantia nigra, pons, medulla and cerebellum of both halves of the brain were studied with the toluidine blue, van Gieson, Hortega, Cajal and Herxheimer scarlet red stains.

The meninges were thickened, cellular and vascular. In some places, especially over the softened area, they were markedly distended. These distended areas were traversed by numerous thin strands of fibrous tissue. The cells seen in the meninges consisted mostly of mesothelial cells. Occasionally, fibroblasts and polyblasts were also seen.

The area of softening (the second and third frontal convolutions) contained only a few islands of brain tissue and was pervaded by numerous blood vessels and strands of connective tissue. The islands of brain tissue were rarefied and contained numerous glia cells. Their ganglion cells were few; some were homogeneously stained; their processes were tortuous and sometimes covered at the margins with numerous dark granules. The cells showed a state of so-called sclerosis. Other cells were not so much changed and contained masses of pigment in their cytoplasm. Some areas were entirely deprived of ganglion cells or nerve tissue. They were replaced by astrocytes and glia fibers, which formed a meshwork covered with an abundance of blood vessels, only an occasional nerve fiber traversing the sclerosed area.

The blood vessels, including the capillaries, were congested and their walls thickened. The endothelial layer usually contained one row of pale cuboid cells which did not protrude into the lumen. The adventitial cells were better stained, were elongated and, as a rule, were provided with two thin processes at their poles. The adventitial spaces were somewhat distended and contained no cells. This was particularly the case in the capillaries. Between the strands of tissue and the blood vessels only a few small round cells were occasionally seen. No polyblasts or cells containing blood pigment (macrophages) were present. With the van Gieson stain, the strands of tissue and the blood vessels appeared pink.

The subarachnoid space was distended and contained lymphocytes, large masses of mesothelial cells, amorphous matter, fragments of pigment and cells, thickened arachnoid trabeculae and, exceptionally, gitter cells.

The softened area was not marked off from the contiguous tissue by any fibrous or cellular wall. The immediately adjoining cortical and subcortical regions were rarefied and gave a reticular appearance. Both ganglion cells and glia cells appeared here to be reduced in number. Reactive phenomena were not observed, either on the part of the glia or on the part of the blood vessels (no new capillary formation). The ganglion cells showed some satellitosis and a moderate degree of neuronophagia. Pigment formation was conspicuous, being both intracellular and extracellular. The pigment was of a greenish color and formed loose agglomerates of flaky substance.

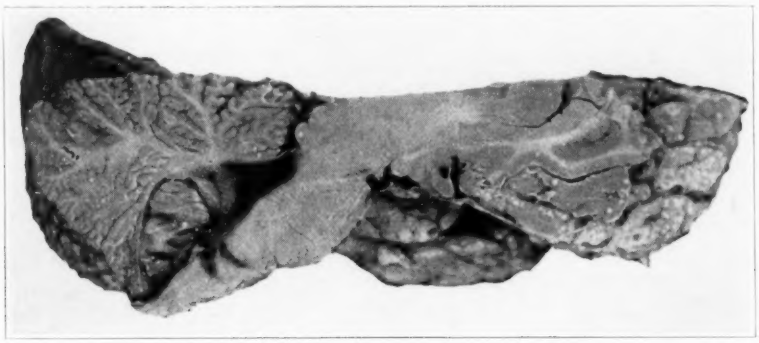
The opposite hemisphere and the cerebral regions situated outside the softened area showed no changes, except for an excessive pigment formation. There was no perceptible increase or decrease of ganglion cells or glia cells nor were there any marked alterations of the blood vessels.

The observations were those of an old softening with cavity formation.

INJURY OF MEDULLA IN PUNCTURE OF CISTERNA MAGNA

A. R. Vonderahe, M.D., and F. C. Haberman, A.B., Cincinnati

Puncture of the cisterna magna apparently is a relatively easy clinical procedure, and the dangers associated with it are readily overlooked. Ayer, from the time of his earliest reports to the present, has not ceased to emphasize the precautions to be taken. A characteristic statement in his papers is as follows: "It must be remembered that those who have performed the puncture reported here thoroughly realize the possible dangers of the procedure. Without a knowledge of the subarachnoid spaces and an appreciation of the physiology of the cerebrospinal fluid, but especially without preliminary experience on the cadaver, cisternal puncture should not be undertaken." [1]



Sagittal section through the brain stem. The cerebellum is displaced caudally in fixation; in addition, there is a pronounced pressure cone. Note the two puncture wounds transfixing the medulla at the level of the olives and the hemorrhage into the fourth ventricle. The scattered gray areas are precipitated from the fixative.

The case reported here emphasizes the necessity of returning to the safeguards recommended by Ayer, especially the requirement of preliminary practice of the technic on the cadaver before an attempt is made on the living patient.

REPORT OF CASE

History.—Eight days prior to the patient's admission to the hospital, a severe earache developed on the right side. Vomiting, severe headache and fever were noted in the course of the next few days. On the day prior to admission, the neck became stiff and the legs were kept flexed. For the past four years the patient had had headache and earache every week or two, accompanied by a purulent discharge from the ears.

From the Department of Anatomy (Neurology), University of Cincinnati College of Medicine.

1. Ayer, J. B.: Puncture of the Cisterna Magna, Report of One Thousand, Nine Hundred and Eighty-Five Punctures, J. A. M. A. **81**:558 (Aug. 4) 1923.

Physical Examination.—There was a purulent discharge from both ears. The neck was stiff and painful on movement. Kernig's sign was positive. The spinal fluid contained innumerable pus cells.

Course.—The patient became comatose. After lumbar puncture, antimeningococcus serum was injected. Later, a puncture of the cisterna magna was performed and a further injection of antimeningococcus serum made. A second cisternal puncture was done, but was unsuccessful; the patient grew worse, and a deep stupor developed. An hour after this procedure, the respiratory rate dropped to 11 per minute; two hours later, respiration was noted as "slow and labored." The respiratory rate continued to fall and reached a rate of 5 per minute. The patient died four hours after cisternal puncture.

Postmortem Examination.—Autopsy was performed one hour after death. The myocardium was pale and mottled. The spleen was soft and swollen; the cut surface showed congestion and prominence of splenic corpuscles. There were areas of diffuse fatty infiltration into the liver. The kidneys appeared swollen and congested.

Gross Examination of the Brain: When the calvarium was opened, the dura mater was found to be slightly, and the pia mater markedly, injected. There was an extensive amount of foul-smelling, green, purulent material over the lateral surfaces of the cerebral hemispheres, as well as over the cerebellum and brain stem. A smear of the pus revealed bacilli and cocci of various types. The brain was again examined after fixation in solution of formaldehyde. There was a subarachnoid accumulation of blood over the pons and medulla. There was a firm blood clot in the fourth ventricle. On sagittal section, two puncture wounds were found, at slightly different levels, traversing the caudal portion of the fourth ventricle in the midline and transfixing the medulla. Their paths were marked by the clotted blood of associated hemorrhages. The gross pathologic diagnosis of the condition of the brain was acute purulent meningitis and puncture wounds of the medulla, at the level of the olives, with hemorrhage into the fourth ventricle.

COMMENT AND CONCLUSION

A case of acute meningitis, in which death occurred four hours after puncture of the cisterna magna, is reported. The respiratory rate dropped to 11 per minute one hour after the procedure and to 5 per minute in three hours; death followed as a result of respiratory paralysis. At autopsy, two puncture wounds of the medulla were found passing through the caudal portion of the fourth ventricle and producing a hemorrhage in this cavity; both traversed the greater portion of the diameter of the medulla at the level of the olives, and hence in an area involving the nuclei of the vagus nerve and including the respiratory center. The clinical diagnosis of acute meningitis was confirmed. The case is reported to emphasize the precautions repeatedly noted by Ayer, especially the requirement of practice of cisternal puncture on the cadaver prior to performance of the procedure clinically.

Obituary

JOSEPH FRANÇOIS FÉLIX BABINSKI

1857–1932

Joseph François Félix Babinski, who has long been one of the commanding figures of modern clinical neurology, died at his home in Paris on Oct. 30, 1932, after a long illness (parkinsonism). For more than thirty years his name has been on the lips of every student of medicine, and his influence has been felt wherever neurology is taught, for not only did he describe the sign of the up-going toe, but he was a great and prolific clinical teacher.

Born in Paris, Nov. 17, 1857, of Polish parentage,* Joseph Babinski, as he generally styled himself, spent his life in France and took his degree in medicine from the University of Paris in 1885. His graduating thesis on multiple sclerosis [1] was a pioneer contribution representing one of the early attempts to correlate the pathologic findings of the disease with the clinical signs. Before his thesis appeared, Babinski had written papers on a variety of subjects; his first, dealing with relapse in typhoid fever, was published in October, 1882.[2] In the following year, he issued case reports on cerebral softening and hydatid cysts of the brain and also published accounts of several cases of malignant conditions.[3] From 1883 on, Babinski continued to publish three or four papers a year until his last illness. After 1890, he confined himself almost entirely to clinical neurology.

Though he had been a disciple of Cornil and Vulpian, it was in the clinic of Charcot that Babinski's abilities were first recognized. Charcot (1825-1893) had become chief of clinic at the Salpêtrière in 1853 and Médecin aux Hôpitaux in Paris in 1856, and in 1872 had succeeded Vulpian as professor of pathologic anatomy. In 1872, also, the chair of "clinic of diseases of the nervous system" was created at Salpêtrière for Charcot, and he continued to occupy this post until his death. Drawn to Charcot as a student, Babinski became his chief of clinic about 1885, and was appointed Médecin aux Hôpitaux in 1890. Charcot died in 1893, and soon after Babinski took charge of the neurologic clinic at the Pitié, a large hospital near Salpêtrière. Here, until a few years ago, he continued to work and to hold his justly celebrated Monday clinics in the Charcot tradition. In 1925, when the centenary of Charcot's birth was celebrated by the Société de Neurologie in Paris, Babinski was president and made one of the principal addresses.[4] He

* Babinski retained the Polish pronunciation of his name, i. e., "Babinski," with the English value of "in" as in information, and French neurologists have generally recognized it.

gave charming reminiscences of his master, but, as was characteristic of Babinski, he suppressed all references to himself and his association with Charcot—and a necrologist is thus left with no statement from Babinski concerning his life during this early period.

It is clear, however, that Charcot's teachings affected him profoundly; indeed, it is sometimes said that Babinski became the conservative embodiment of Charcot himself. He, of course, lacked the tendencies toward the dramatic that so vividly characterized Charcot, but he nevertheless had the faculty of holding the attention of the host of students and visitors that regularly thronged his amphitheatre, especially for the Monday clinics.[5] Babinski's logic was more rigorous than that of Charcot, and his observations more detailed and search-

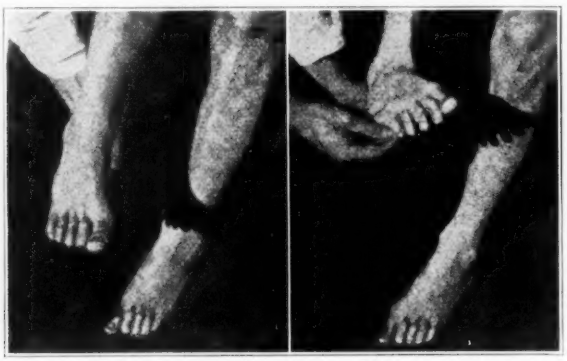
Babinski as a young man (about 1895).

ing, but some felt that his insight, particularly into the psychologic background of mental cases, was more restricted.

The sign which made Babinski's name one of the chief eponyms of medicine was first described in a preliminary note before the Société de Biologie on Feb. 22, 1896. It was a simple statement that, "in certain cases of 'paralysis,' the toes on the affected side, instead of flexing when the sole is stimulated, execute an extensor movement on the metatarsal."[6] Two years later[7] he gave a full account of this phenomenon, and his excellent description summarized the important features of the normal and pathologic plantar reflex in human beings. To his description there has been little to add in later years, although the "*signe de l'éventail*," or fanning of the outer toes, which is often

part of the reflex, was not mentioned in the original paper, but was separately described in 1903.[8] Babinski was an ingenious amateur photographer, and his papers were likely to be illustrated by striking snap-shots of gaits, postures or pareses. This is particularly well exemplified by the illustration in his paper on the *signe de l'éventail* where the fanning is cleverly brought out by the shadow of the toes against the other leg.

Babinski's description of the extensor plantar response was quickly brought to the attention of the English speaking medical world by the paper of James Collier, published in 1899,[9] in which the functional significance of the normal plantar reflex and its pathologic counterpart, the Babinski sign, was first fully appreciated. An immense literature has since grown up concerning abnormal plantar reflexes, and it is now firmly established that Babinski's sign provides positive indica-



Photograph illustrating the sign of fanning of the toes.[8]

tion of disease or injury of the pyramidal pathway, and it stands as of equal importance with the Argyll Robertson pupil as a sign of a structural lesion of the central nervous system. More recently, the sign of Babinski has proved of great theoretical interest, since it has been found absent in the lower members of the primate scale (i. e., monkeys and baboons) after complete destruction of the pyramidal pathways, but strongly present in the higher anthropoids (chimpanzees) after lesions of the corticospinal system, thus giving experimental proof that the pyramidal system is more completely dominant in these forms.[10]

In addition to his studies of cutaneous reflexes, Babinski made important contributions to many other fields of clinical neurology. In the exposé of his scientific works, published in 1913,[11] more than two hundred papers are listed and summarized. Among the papers on pure physiology and histology, one finds that in 1886 he described the muscle spindle and pointed out that it was a normal constituent of muscle, and

was not, as some had supposed, found only in amyotrophic sclerosis;[12] at that time, however, he did appreciate the spindle's sensory function.

Babinski's analysis of cerebellar symptomatology is classic, and he is largely responsible for introducing the modern terminology. His first paper on the subject in 1899[13] laid the foundation of the conception of "asynergia" as being the underlying symptom of cerebellar deficit, i. e., an inability to carry out complex motor acts involving the harmonious cooperation of separate muscle groups. He pointed out that in cerebellar disease, movements become dissociated: the onset is delayed (cerebellar "catalepsy"), but once started it tends to continue beyond its period of usefulness, with the result that the extremity overshoots the mark ("hypermetria"); furthermore, there is inability to perform alternating movements such as pronating and supinating the arms ("adiadokokinesis"[14]). This brilliant analysis of the symptoms of cerebellar deficit has stood for more than thirty years, and clinical literature would be spared much if there were more general adoption of Babinski's terminology.

It is often forgotten that Babinski and Nageotte were largely responsible for recognizing the physiologic basis of locomotor ataxia[15] and they gave the true explanation of the loss of tendon reflexes in this condition. In 1899, with Albert Charpentier,[16] he described the abolition of the pupillary response to light in cases of cerebral syphilis.

Babinski also contributed to the progress of neurologic surgery and, in 1911, localized and removed the first spinal cord tumor to be operated on in France.[17] His lifelong interest in the localization of cerebral tumors also contributed to the advancement of neurosurgery, but this has come largely through the energy of his pupils, de Martel and Clovis Vincent. The year before Frölich described the adiposo-genital syndrome in the male, Babinski published (1900) a remarkable case report entitled "Tumor of the Pituitary Body without Acromegaly and with Arrested Development of the Genital Organs."[18] He is thus entitled to priority in the description of this important syndrome in so far as it relates to females.

In reviewing his contributions in the broad field of medicine, one must also mention Babinski's work on hysteria.[19] Under the stimulus originally received from Charcot, Babinski devoted much time and energy to the elucidation of hysteria and other related mental conditions. He was the first to give satisfactory criteria for differentiating hysterical manifestations from those produced by organic lesions of the nervous system, i. e., he pointed out that superficial and deep reflexes are normal in hysterical patients. His celebrated definition of hysteria ("pithiatisme") deserves to be quoted in its original form:[19c] "L'hystérie est un état pathologique se manifestant par des troubles qu'il est pos-

sible de reproduire par suggestion, chez certains sujets, avec une exactitude parfaite et qui sont susceptibles de disparaître sous l'influence de la persuasion (contre-suggestion) seule." Babinski recognized the importance of conflict in the etiology of neuroses, but he did not commit himself, as has his contemporary Janet, to the theory of dissociation. In handling hysterical cases, particularly the war neuroses,[20] his success was outstanding and deserves to be more widely known.

In spite of his many activities he gave much of his time as an editor of the *Revue neurologique*, with which he was associated from 1911 to 1932. He was honored by many foreign societies and had been an honorary member of the American Neurological Association since 1924.

Babinski was a large man, more than 6 feet in height, almost formidable in appearance, but slow in movement and in speech. He was always attentive to inquiries and never seemed to hurry when patients were telling their histories. He watched them attentively and often made up his mind concerning their illness as a result of this preliminary scrutiny. His subsequent neurologic examinations, however, were always detailed, with few words of explanation, and he had an uncanny faculty for bringing out abnormal reflex changes, often to the humiliation of previous examiners. One of Babinski's pupils [21] records the following anecdote which serves to illustrate his personal characteristics. One morning, Babinski, while examining a patient at his hospital, surrounded by students, was asked by one of them, "What is your diagnosis in this case?" Babinski responded very simply, "I do not know. I am investigating. Do as I do and we shall talk about it again."

Babinski's life should be an inspiration, particularly to the younger neurologists, for here was a scientist who gained preeminence entirely in the clinical field. He had that rare trait, curiosity, which impelled him to seek an explanation for unusual observations. Extension of the large toe in pyramidal disease had always existed, but it remained for Babinski to point out the cause. His life and his work illustrate that research is not necessarily confined to the laboratory, but that some of the greatest achievements in neurology are possible by keen clinical observation.

No more fitting estimate of Babinski could be found than that published by Charpentier in a Paris newspaper the day after his death.[21] It runs thus:

> Je crois qu'il est rare d'entendre un aveu d'ignorance dans la bouche d'un maître qui enseigne la jeunesse. Quelle franchise dénuée de tout respect humain chez ce savant dont je constatais chaque jour l'avidité de connaître et l'angoisse de se tromper! Tous ceux qui venaient écouter ses conférences l'admiraient pour son esprit d'observation prodigieux; on l'estimait pour cette belle ordonnance des âmes droites qui cultivent la vérité. Quand il ne réfléchissait pas à des problèmes

de pathologie, il écoutait les bruits du monde comme on regarde un paysage. Cette allure simple, cet amour des humbles, ce culte de la vie qui lui faisait passer le soir une heure de délassement au Foyer de la Danse, que vous donniez de charme à ce géant aux veux doux! Je veux taire, pour rester fidèle à l'enseignement d'une si belle vie, tout le bien que Babinski a fait autour de lui, en plus des bienfaits immenses que son génie a répandus sur le monde pour sauver les malades.

JOHN FULTON, M.D.

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15. ——Sur un cas de tabes à systématisation exceptionelle (en collaboration avec Nageotte, J.), Compt. rend. Soc. de biol. **59**:80, 1905.

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21. Charpentier, Albert: Babinski, Figaro, Dimanche, 30 Octobre, 1932, p. 2.

News and Comment

EXHIBIT ON NERVOUS AND MENTAL DISEASES AT MILWAUKEE

The Section on Nervous and Mental Diseases of the American Medical Association has appointed a special committee on section exhibit to cooperate with the Committee on Scientific Exhibit in promoting an exhibit on nervous and mental diseases for the Milwaukee Session of the American Medical Association, June 12 to 16, 1933. The special committee consists of T. J. Heldt, chairman, Detroit; E. D. Bond, Philadelphia, and G. B. Smith, Godfrey, Ill. The closing date for applications is February 13. Application blanks for the exhibit may be obtained from members of the committee or from the Director, Scientific Exhibit, 535 North Dearborn Street, Chicago.

Editorial

SURGERY OF THE SENSORY ROOT OF THE FIFTH NERVE

No more brilliant chapter in the advances of knowledge of therapeutics can be found than in the remarkable results obtained in surgical intervention in the nervous system. Less than three decades ago the removal of a tumor of the brain was looked on with dread, while now the mortality in certain types of cerebral lesions is less than 10 per cent. In recent years the sympathetic nervous system has received a great deal of attention, and while its surgical treatment has not yet been placed on a firm foundation, nevertheless, it promises to give excellent results.

Perhaps because of the necessity of the relief of pain, particularly in the face, operations on the fifth nerve have always aroused great interest. This is emphasized by the three papers on this subject which appear in this issue and which more or less summarize the brilliant results that have been obtained by section of the sensory root for the relief of tic douloureux. Knowledge of this subject, however, is by no means complete, for the cause and pathology of tic douloureux are unknown. The causes and relief of so-called atypical pain still remain a mystery, but the subtotal operation on the sensory root for tic douloureux, as developed by Frazier from a suggestion originally made by Spiller, undoubtedly remains the operation of choice.

There has been some controversy regarding the credit for this operation. The first mention of such a possibility was by Ferrier, who in 1890, in a discussion of a paper on the "Removal of the Gasserian Ganglion for Severe Neuralgia" by William Rose,[1] stated that "the pathology of neuralgia was obscure and in many cases it may be of central origin. Section of the nerve above the ganglion might cause an ascending degeneration and thus lead to relief by producing atrophy of the center." While it is difficult to interpret Ferrier's meaning at this date, it is presumable that he meant sectioning of the sensory root with atrophy of the center in the pons or higher. No attention was paid to Ferrier's remark by Horsley, who in the following year avulsed the sensory root from the pons in a single case, nor did he make any reference to Ferrier in his subsequent paper published in 1897.

In 1891, in a series of papers, Victor Horsley with James Taylor and Walter S. Coleman [2] suggested division of the fifth nerve behind

1. Rose, William: Lancet **2**:914, 1890.

2. Horsley, Victor; Taylor, James, and Coleman, W. S.: The Various Surgical Procedures Devised for the Relief or Cure of Trigeminal Neuralgia (Tic Douloureux), Brit. M. J. **2**:1139 (Nov. 28); 1191 (Dec. 5); 1249 (Dec. 12) 1891.

the gasserian ganglion. After some preliminary dissections and experiments on a monkey, he performed the operation on a patient in whom there had previously been removed a portion of the inferior dental and infra-orbital nerves. "The operation presented no special difficulty beyond that of being very tedious." On exposing the nerve he avulsed it, but the patient died seven hours afterward, obviously from shock. The removal of the gasserian ganglion was thought impossible, for Horsley stated: "I have already shown that the ganglion cannot be wholly removed from its bed but only a small portion."

Subsequently, in 1897, in the *Clinical Journal*[3] and in a reprint of the same article in a separate pamphlet, Horsley made the definite statement: "There can be no doubt, I think, that the Krause-Hartley operation as practised now is the scientific operation for trigeminal neuralgia, and ought always to be performed at once where the disease is intractable to ordinary remedies, and where the pain affects more than one branch." Throughout this article, with the exception of a reference to his operation of dividing the sensory root in 1891, he does not mention its repetition. However, after discussing the avulsing of the sensory root, he states: "Experience derived during the six years that have elapsed since the publication of that paper leads me to believe that the difficulties which the subject presented in 1891 can in a great measure be now avoided, and the course of action that we propose to the patient rendered more certain." It would seem, in view of his subsequent statements, that he refers to the whole subject rather than to a particular procedure, for he later states: "The object of the following pages is to take advantage of our further knowledge of this subject, especially in the light of the greatly improved operative treatment of this disease by . . . the Krause-Hartley operation."

In November, 1898, Spiller[4] made the following statement in the *American Journal of the Medical Sciences:* "If it could be shown that the sensory root of the Gasserian ganglion does not unite after its fibers are divided, we should have a fact of great importance. Division of this root would probably be a less serious operation than the removal of the entire ganglion, and might have the same effect in the relief of pain, but the surgical difficulties might be insurmountable. Experiments on animals to determine whether or not the sensory root of the Gasserian ganglion unites after section of its fibers might result in a lessening of the great mortality now existing in operations on the ganglion." At that time Spiller was unaware of Sir Victor Horsley's previous

3. Horsley, Victor: Treatment of Trigeminal Neuralgia, Clin. J. **11**:21 (Nov. 3) 1897; also, London, Medical Publishing Company, Ltd., 1898.

4. Keen, W. W.: Remarks on Resection of the Gasserian Ganglion. Spiller, W. G.: Pathological Report on Seven Ganglia Removed by Professor Keen, Am. J. M. Sc. **116**:532 (Nov.) 1898.

operation. However, when his attention was called to it, in a paper by Spiller and Frazier[5] published in the *University of Pennsylvania Medical Bulletin,* December, 1901, he made the statement: "I believe that Horsley is the only one who, before Dr. Frazier, has divided the roots of the trigeminal nerve without removing the ganglion."

If it is difficult to reconstruct a situation only a few months old, it is much more difficult for the present generation of neurologists to understand the state of knowledge thirty years ago. Operation on the ganglion at that date was exceedingly grave; the mortality was given by Tiffany as 22.2 per cent. At that time there was a question as to whether regeneration in the sensory root was possible. On account of the studies of several investigators and especially those of Ballance and Stewart, in order to place the operation of division of the sensory root on a sound foundation and to exclude the possibility of regeneration of the sensory root after division, seven specimens of the gasserian ganglion and its roots, removed from as many dogs on which division of the sensory root had been performed by Frazier, were examined by Spiller. This was followed by a whole series of studies on the morphologic aspect of the gasserian ganglion. The operative technic was refined step by step, and, to quote Dandy:[6] "There have been few greater triumphs in surgery than the Krause operation in its final form as developed by Spiller and Frazier for the permanent cure of one of the worst pains with which mankind is afflicted. The mortality rate has been gradually reduced to 0.5 per cent in the hands of the most skilled surgeons."

Without failing to give credit to Horsley, it seems obvious that the development of the operation on the sensory root of the fifth nerve to its present state is largely the result of the excellent work of Spiller and Frazier.

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Abstracts from Current Literature

THE MECHANISM OF ACCOMMODATION, FACTS AND FANCIES. W. H. LUEDDE, Arch. Ophth. **7**:40 (Jan.) 1932.

The problem of accommodation has been one over which physiologists and ophthalmologists have worked since the theory was presented. Speaking of a well established, time honored theoretical solution, the author states: "It is a theory that through its age and honorable heritage has almost achieved the authority of fact, yet it lacks 'the complete reasonableness of natural phenomena.'" Or, as Ovio put it: "This state of elasticity of the crystalline lens in repose has at first approach several things that seem paradoxical in spite of the great authority of Helmholtz, who made it the foundation for his theory of accommodation." So many volumes have been filled with experimental and clinical observations, and with mathematical calculations pertaining to this mechanism, that a satisfactory summary of recorded facts seems hopeless of attainment on account of contradictions. There is, however, consolation in knowing that actual facts never contradict and that they can be coordinated by the elimination of error.

Langenbeck (1849), Cramer (1853), and Helmholtz (1853) are credited with priority in furnishing objective proof that the changes within the human eye incident to accommodation for near vision are essentially and exclusively alterations in the form of the crystalline lens. Half a century earlier, Thomas Young (1801), by two original and well known experiments, had eliminated alterations in the convexity of the cornea or increase in the length of the eyeball as possible factors in the mechanism of accommodation in his own eye.

Carl von Hess classified what takes place in a normal youthful eye in changing from a position of rest to one of near vision. The following is quoted from an authoritative posthumous publication by him: "1. The pupil becomes smaller. 2. The anterior vertex of the lens moves forward so that the anterior chamber becomes more shallow in its central zone. 3. The peripheral segment of the anterior chamber does not become noticeably shallow and in many eyes an actual increase in its depth through retraction of the peripheral zone of the iris may be noted. 4. The convexity of the visible anterior pupillary segment of the lens is considerably increased. Whether the convexity of the posterior surface of the lens is increased is not entirely certain. 5. When the strongest possible effort of accommodation is made, the crystalline lens will sink approximately from 0.25 to 0.3 mm. in response to gravity according to the position of the head, temporally, nasally, frontally or infra-orbitally toward the ciliary body. 6. By short jerking movements of the eye the lens may be seen to tremble. If the eye is not moved, even a maximal accommodative effort fails to produce any trembling of the lens. The distinctness and degree of the trembling of the lens vary greatly in different persons. In many cases the trembling is so marked that the sector of the overlying iris also trembles. 7. Observation of the lens spectrum of the observer's own eye will show that when an accommodative effort has reached a certain degree there is a sudden transposition upward of the entoptic lens figure (particularly noticeable in single outstanding points of the image corresponding to tiny lenticular opacities). When the accommodation is then suddenly relaxed, a similar movement downward is to be noted. During and immediately after short jerking movements of the eyeball, while the accommodative effort is at its height, the trembling of the entoptic image of the lens may be noted."

Hensen and Voelckers demonstrated, without question, that the ciliary body does not change its position with reference to the scleral wall. Tips of needles were inserted through the sclera into the ciliary body, and when electrical excitation was applied no forward or backward movements occurred. Similarly, needles

in the macular region at the posterior pole remained unmoved. Voelckers demonstrated that the point of fixation is at the forward extremity and that its contraction produced forward movement of the choroid throughout the circumference of the eyeball.

Von Hess and all others who have sought to uphold von Helmholtz's suggestion of a mechanism of relaxation to account for the changes in the form of the lens during accommodation have endeavored in theory to connect the forward movement of the choroid seen at the very beginning of contraction of ciliary muscle with the evident relaxation that can be demonstrated only at the highest stage of this action. This final relaxation with the greatest effort of accommodation is easily explained. It is not due to the advance of the choroid, but is the result of the narrowing of the inner ring of ciliary body incident to the regular thickening of muscular contraction which must release the suspensory fibers of the zonule that are attached just behind the corona ciliaris. This narrowing of the inner ring of the ciliary body is well depicted by Hess in sketches of human eyes treated with atropine and with physostigmine. It appears to be entirely independent of the mechanical activity during the ordinary range of accommodation. Probably the only helpful effect which this final relaxation provides for the function of accommodation is the forward movement of the lens when looking downward which Hess described.

The most popular fallacy is the assumption that the lens is made up of an elastic substance. Helmholtz, Schweigger, Hess, Hensen and Voelckers, Collins, Finchman, Holloway and Cowan have written pro and con on this. Hess ruled that there can be no thought of elasticity of the lens substance. Holloway and Cowan stated: "Sufficient evidence has not been brought forward to establish a uniformity of opinion concerning the extent of the zonular lamella." Collins stated: "There are thus developed in the growth and expansion of the eye forces dragging on the posterior part of the lens capsule forwards and outwards, and on the anterior part of the lens capsule backwards and outwards. The effect of this on the elastic curved lens fibers is to cause them to become more bent and kept in a state of tension. A state of tension occurs which is only relaxed when by the contraction of the ciliary muscle the suspensory ligament is slackened and the pull on the capsule relieved."

The author states: "The presence of elastic fibers in the lens capsule raises the question whether these elastic fibers are there to cause increased convexity of the lens or to flatten its surfaces in a state of rest. The latter would be the more natural physiologic function."

Von Hess seemed to close the subject well when he demonstrated that a youthful crystalline lens which lies free of attachments and surrounded by air is noticeably flattened by its own weight. It shows that the capsule of a young lens at its best, so far as the range of accommodation is concerned, does not have enough power (elasticity) to produce a convexity of the surface of that lens sufficient to resist its own weight when placed on a flat surface. It seems out of order, therefore, to assign to the relatively feeble elasticity of the lens capsule the major rôle in accommodation.

The question of vitreous acting on the posterior surface of the crystalline lens solely by hydrostatic pressure has also been presented by Cramer and Donders, producing a mechanism that must have an important rôle. This rôle of the vitreous cannot be lightly dismissed. The vitreous has a definite structure, and its probable influence on the form of the lens during accommodation was demonstrated by Park Lewis eleven years ago. These two structures, i. e., the vitreous and the lens, may be made to react effectively the one against the other without increase of intra-ocular tension as long as they are surrounded by intercommunicating spaces and there is no increase in intra-ocular contents. It has been demonstrated that they react as tissues and not within the narrow limits of "hydrostatic pressure."

Virchow was methodical in his discussion of the vitreous as a tissue. As the author states, "One cannot gainsay the probability that, if the convex anterior

segment of the vitreous that surrounds the fossa patellaris is pressed against the equatorial zone of the lens, the soft cortex of the periphery of the lens will be pushed forward and axipetally, and increased convexity of the anterior surface will result."

Hensen and Voelckers in their experiments noticed changes in the shape of the vitreous with excitation of the ciliary nerves, but, as Luedde stated, "as these facts seemed contradictory to the general scheme of relaxation postulated by the accepted theory, a natural tendency developed to disregard or evade them and sometimes, by much involved explanations, to indicate their irrelevance."

According to Salzmann, the vitreous is fixed most firmly at the ora serrata and to the ciliary epithelium in a zone about 1.5 mm. broad immediately adjacent to the ora serrata.

In view of this direct attachment, only a fact-defying fancy could deny the probability of a general forward movement of the anterior segment of the vitreous, more especially at its periphery, as soon as contraction of the ciliary muscle occurs.

The work of Heine, Hess and Beer showed that if the vitreous does play a part in accommodation, it must mean movement of structural tissue and not mere hydrostatic transfer. It is also of interest that the vitreous is held against the lens rather firmly by two factors: (a) the ligmentum hyaloideocapsulare (a firm anatomic union) and (b) the sustained contraction of the ciliary muscle through its traction on the "base of the vitreous." This explains some of these occurrences in the last stage of accommodation.

Von Pflugk, in a study of accommodation in the eyes of birds, monkeys and men, presented a series of photographs of frozen sections of the eyes, showing changes in the form of the lens of accommodation in entire accord with what might be expected if the vitreous were pressed against the lens. Von Pflugk concluded that the lens with increased accommodation departs more and more from the form postulated by von Helmholtz for the accommodated lens. Fischer, in work on the same subject, did not wholly agree with von Pflugk's findings. As Luedde stated, however: "von Pflugk's findings must stand, in that he eliminated certain possible errors which Fischer failed to take into consideration." Gullstrand also discussed the work of von Pflugk, but did not agree or disagree with the findings. Zeeman seemed to agree with the findings of von Pflugk. Here, however, Gullstrand also took exception to Zeeman's findings. Luedde, however, explained Gullstrand's exceptions. It seems that Gullstrand observed Zeeman's findings in senile lenses by looking in a direction nearly along the equator of the core. As Luedde showed, however, Gullstrand's apparent confusion of the static phenomenon of senile lenses with observations made during active accommodation tends to make his (Gullstrand's) rejection less convincing.

The author illustrates with sketches changes that occur in a subluxated lens under pilocarpine. In all cases, the lenses seemed to drop away from the center of the pupil. This, with photomicrographs of animals killed by poisoning with atropine and physostigmine, seems to indicate pressure forward of the vitreous body against the equator of the lens with sufficient force to cause increased convexity by displacement of the lens substance away from the equator toward the center.

Relative to increased convexity of the anterior surface of the lens, Gullstrand rejected Tscherning's assumption that the tension of the zonule is sufficient to form anterior lenticonus. Einthoven, however, confirmed Tscherning's opinion by his experimental work. He discovered that a pull with forceps at opposite ends of a diameter increased or decreased the anterior convexity of the lens, according as he pulled more backward or more forward, respectively. Salzmann stated that "This same principle applied to the human eye, when the vitreous is pressed against the lens by forward traction of the ciliary muscle, will so modify the static traction of the suspensory fibers of the zonule on the anterior capsule that they will also pull backwards and thereby increase the convexity of the anterior surface of the lens." It is interesting that von Hess considered this probability.

Attempts to determine definitely the detailed changes of form for the anterior and posterior lens surfaces by measurements of Purkinje's images have been disappointing, owing to a lack of harmony in fact finding and in interpretation. Measurements of both the anterior and posterior surfaces have not been reliable. The conclusions of Gullstrand, a master of physiologic optics, offered Luedde little inducement to review in detail the many pages of mathematical formulas by which measurements of these surfaces are carried on. Gullstrand proposed an intracapsular mechanism of accommodation as a mathematically necessary consequence of the change of form and of increase of the refracting power.

Gullstrand, Tscherning and Schoen agree in part and disagree in part as to the factors connected with this theory of physiologic optics.

The next problem to be considered is that of sympathetic and parasympathetic innervation. Here also controversy has arisen. Don Joseph and Poos demonstrated relaxation of the sphincter and contraction of the dilator fibers, but attempts by other investigators to secure similar results with various animals have failed. Hess and Heine indicated that the mechanism of accommodation depends on innervation of the ciliary muscle by the motor oculi. The thought of Morat-Doyon that the sympathetic adjusts the eye for distance and the motor oculi for near vision was not verified. Hartgraves and Kronfeld, in a study of the use of sympathomimetic drugs to increase the effect of atropine, seemed to show that the effect of atropine on the ciliary body cannot be increased by any method.

The author concludes with three pointed statements: First, only one preposterous assumption seems to stand in the way of a harmonious coordination of all facts concerning the mechanism of accommodation, namely, the assignment of an impossible rôle to the physiologic property called elasticity. Second, clinical ophthalmology presents a group of problems that wait more or less on a better understanding of the actual mechanism of accommodation; therefore, an earnest consideration of this mechanism as an abstract problem seems fully warranted. Third, certain formulas in physiologic optics built on the relaxation theory require reconstruction.

SPAETH, Philadelphia.

CLINICAL AND EXPERIMENTAL BASIS FOR SURGERY OF THE PELVIC SYMPATHETIC NERVES IN GYNECOLOGY. RENÉ FONTAINE and LOUIS G. HERRMANN, Surg., Gynec. & Obst. **54**:133 (Feb.) 1932.

The authors present twenty-two cases of dysmenorrhea or pelvic plexalgia treated by resection of the superior hypogastric plexus (presacral nerve). They review at some length the anatomic and physiologic basis for operations on the pelvic sympathetic nerves in gynecology. They "feel that the hypogastric plexuses carry the important pathways of sensation from the internal genital organs to the medullary centers and that the section of the superior hypogastric plexus (presacral nerve) above the hypogastric ganglion is a safe, simple and efficacious way of interrupting these pathways in the treatment of the functional type of dysmenorrhoea as well as a method of relieving other forms of severe pelvic pain."

The cases in which pelvic sympathectomy is indicated are divided by the writers into three main groups: *A*, cases in which no organic lesion of the genital organs can be found to account for the pelvic pain, i.e., functional dysmenorrhea; *B*, cases with slight pathologic processes in the pelvis which do not react favorably to ordinary gynecologic treatment, i.e., sclerocystic degeneration of the ovaries and persistent pelvic pain following some previous operation, and *C*, cases in which the pathologic lesion is known but has been found to be too extensive for surgical removal, i.e., inoperable neoplasms in the pelvis giving rise to severe pain.

"Group A: The functional type of dysmenorrhoea characterized by severe crises of pain immediately preceding or during the menstrual period that resist the ordinary gynecological therapeutics have been found to react most favorably to the operations upon the pelvic sympathetic nerves." This favorable group also

includes those cases of genital hyperexcitability that have crises of hydrorrhea and congestion of the pelvic organs, accompanied by severe pain.

"Group B: The great majority of cases naturally fall into this group for it is comparatively rare to find true functional dysmenorrhoea without the slightest demonstrable pathological lesion or anatomical abnormality of the internal genital organs."

"In all cases of mobile retroversion of the uterus or slight sclerocystic degeneration of the ovaries, proper medical and non-operative gynecological treatment should always be given a fair trial. If, after a reasonable length of time, there is no improvement in the subjective symptoms the question of operative interference should be considered." Palliative operations, such as partial resection of an ovary or unilateral oophorectomy, often do not relieve the pelvic pain in sclerocystic degeneration of the ovaries. This type of patient is usually completely relieved of pelvic pain by simple section of the superior hypogastric plexus, without sacrifice of any of the internal genital organs and without influencing subsequent marriage and ability for child bearing. In cases in which definite anatomic lesions are present, which might account for part of the pelvic pain, the authors do not advise section of the superior hypogastic plexus alone. They believe that at the time of the laparotomy the retroverted uterus should be suspended in the normal position and the cystic portion of the ovary removed, but the pelvic sympathectomy should remain the most important part of the operation.

Group C: The severe pain of inoperable neoplasm in the pelvis or, more rarely, of sclerosis in the pelvis after intensive radiation by radium or deep roentgen therapy should be treated surgically, even though there is no hope for operative cure of the neoplasm. Most of the numerous procedures for the relief of such pain have failed to give uniformly satisfactory results. In the absence of metastases to the vertebrae and of typical root radiation of the pain, the authors believe "that it is advisable to verify the extent of the neoplasm and, if possible, determine the cause for the severe pain, and then perform the complete sympathectomy."

The writers mention four main types of sympathectomy that may be employed to treat the various painful disturbances in the female pelvis: (A) section of the superior hypogastric plexus, (presacral nerve), (B) section of the ovarian nerves, (C) periarterial sympathectomy of the internal iliac artery and (D) section or removal of the lower part of the lumbar sympathetic chain of one or both sides.

For hypogastric plexalgia, the authors point out the greater simplicity and equally good results of section of the superior hypogastric plexus (presacral nerve) as originally proposed by Cotte (1925), in comparison to periarterial sympathectomy of the internal iliac artery (Leriche, 1921), which is suitable, however, in cases of trophic disturbances of the external genital organs, especially of kraurosis vulvae. For degeneration of the ovaries, the method of Lhermitte and Dupont (1926), consisting of isolation and resection of the nerves in the utero-ovarian ligaments is difficult to perform, and it is difficult to be certain that all the nerves are severed. Clinically, it is sometimes impossible to differentiate between the pelvic pain due to disturbances in the ovaries and that due to disturbances in the superior hypogastric plexus. The authors believe that section of the superior hypogastric plexus should be the operation of choice for the relief of "pelvic plexalgias."

The authors report twenty-two cases of resection of the superior hypogastric plexus (presacral nerve) performed on twenty-two young women suffering from some form of severe pelvic pain. In one case only was resection of the superior hypogastric plexus performed. In all the other cases "the associated anatomical derangement or slight pathological lesions" were corrected at the same operation. Abstracts of these cases from the clinic of Leriche are given. Fifteen of the twenty-two patients have had repeated follow-up examinations over a long period. Six failed to return, but on discharge were completely relieved of pelvic or

abdominal pain. One died on the second postoperative day. Thirteen of the fifteen patients who have been followed admit that they have secured relief from all pelvic or abdominal pain. One has been free for over four years, another for two and one-half years. Two of the fifteen derived only slight or no benefit. The writers think that these results justify resection of the superior hypogastric plexus as a means of relieving severe pelvic and lower abdominal pains.

Section or removal of the lower lumbar sympathetic chain on one or both sides should be used as an adjunct to other pelvic sympathectomies. For complete relief of severe pain due to inoperable pelvic neoplasms, Leriche (1925) suggested resection of the superior hypogastric plexus (presacral nerve) from its origin at the intermesenteric plexus to the lower part of the aortic bifurcation, together with resection of both lumbar sympathetic chains. Because simple section of the superior hypogastric plexus does not always give complete relief, the authors advocate the more complete removal of the pelvic sympathetic nerves. No great risk is added with the complete pelvic sympathectomy of Leriche, and the authors state that "one can be quite certain of complete relief from the most intolerable pelvic pains." The writers prefer complete pelvic sympathectomy to chordotomy, since it gives relief without sacrificing any of the normal protective reflex pathways. Six cases of varying degrees of pelvic sympathectomy are presented, and illustrate the results that Leriche has obtained with complete pelvic sympathectomy for the relief of the intolerable pain of inoperable pelvic neoplasm.

The authors' conclusions, slightly condensed, are: In the twenty-two cases of dysmenorrhea or pelvic plexalgia, there has been complete and lasting relief from the pelvic pain in the great majority following resection of the superior hypogastric plexus (presacral nerve). Disturbances of micturition following this operation are rare. The superior hypogastric plexus is essentially a pathway for afferent impulses from the internal genital organs. The excruciating pain that is frequently associated with inoperable neoplasms in the pelvis can be completely relieved by an extensive pelvic sympathectomy. In all cases, even those in which the most extensive pelvic sympathectomy was performed, there have been no serious complications that could be attributed to the operation: no motor paralysis, no ascending urinary infection due to paralysis of the bladder and no sensory disturbances of any part of the skin. Since this operation also gives the surgeon an opportunity of verifying the extent and nature of the neoplasm at the same operation, we believe that it should be used in preference to chordotomy for the relief of intolerable pain in the pelvis due to an inoperable neoplasm of any of the pelvic organs, provided the pain is not due to metastatic foci in the vertebrae.

The authors have described the indications and surgical technic for various forms of pelvic sympathectomy. They review the literature concerning the anatomy and physiology of the pelvic autonomic nervous system, particularly as it applies to gynecologic surgery. In all of their twenty-two cases of dysmenorrhea or pelvic plexalgia except one "the associated anatomical derangement or slight pathological lesions" were also corrected at the same operation; nevertheless the authors believe that the results justify resection of the superior hypogastric plexus for severe pelvic and lower abdominal pain; this is in accord with other writers. On the whole, their article reviews well the question of pelvic sympathectomy in the field of gynecology.

ELVIDGE, Montreal, Canada.

THE CELLULAR STRUCTURE OF THE GLOBUS PALLIDUS AND NUCLEUS BASALIS IN MAMMALS AND IN MAN. ERNST GRÜNTHAL, Jahrb. f. Psychol. u. Neurol. **44**:403, 1932.

In primates the globus pallidus consists of two parts: (1) the dorsomedial (*a*) and (2) the basocellular (*b*). The former consists of two segments and is the only part that has always been designated in primates as the pallidum. Part *a* is usually well developed, whereas part *b* shows definite evidences of regression. In

lower mammals, part *b* occupies a considerable portion of the basal and lateral pallidum. The author believes that this part is homologous with the nucleus basalis (nucleus substantiae innominatae or nucleus ansae lenticularis) in man. In favor of this theory is the similarity of the cells of this nucleus throughout the mammalian series. In all of them the cells are of considerable size, stain well, and contain abundant Nissl substance. On the other hand, it is noteworthy that in this respect there is a great resemblance between the guinea-pig, dog and primates. It is also striking that as one ascends the mammalian scale from guinea-pig, dog and macacus to the chimpanzee, these cells become smaller in spite of the gradually increasing size of the brain, whereas in man with his unusually large brain these cells are also the largest. Furthermore, pallidum *b* is rudimentary in primates in those areas which in lower mammals are always included in the pallidum *b*. The author agrees with de Vries, according to whom the paleostriatum consists of the globus pallidus and the nucleus basalis, and that the latter cannot always be sharply distinguished from the former; as a matter of fact, this nucleus does not occur even in insectivora and in the mouse.

Recently, Spatz has shown that in man the globus pallidus and the nucleus basalis are two different structures, cyto-architectonically as well as myelo-architectonically. They have different histochemical properties and different tendencies to disease. Grünthal also finds that in man, as well as in lower mammals in which there is as yet no morphologic separation of the pallidum, the *b* portion of this structure differs histochemically from the *a* portion.

The remarkable uniformity of structure of the pallidum in the individual subgroups of the lower mammals and the better development of the *a* portion in primates is, from a comparative point of view, in marked contrast to the development of the hypothalamus. In all series of animals the hypothalamus consists of a uniform group of prominent nuclei situated orally and caudally. There also exist numerous other nuclear formations which show a tendency to extensive regression and simplification as one ascends the animal scale. At the same time the longitudinal and lateral development of the thalamus remains measurably behind the development of the cerebrum. In the guinea-pig the length of the hypothalamus to that of the cerebrum is as 1 : 3, and in man as 1 : 7. The pallidum, on the other hand, develops in direct proportion to the length of the cerebrum, being almost always one-fifth the size of the latter. In contrast to the dual type structure of the pallidum, the hypothalamus shows throughout the mammalian series, according to the degree of differentiation, a three type structure. The most complex hypothalamus, structually, is found in the lower groups, up to, and including, the rodents. In Carnivora, Ungulata and in the lower apes the hypothalamus is, relatively speaking, moderately developed, whereas in the higher apes and in man, though simple in structure, it is unusually well developed. It may therefore be said that the structure of the hypothalamus is characteristic for each individual animal series and subgroup and in some way must be basic and essential for the existence of that particular animal or series. Such, however, is not the case with the pallidum. In contrast to this there is phylogenetically a certain parallelism between other parts of the brain. Thus, as Monakow has shown, the main portion of the red nucleus increases in size with the increase in development of the cerebral cortex. This is also true of the dentate nucleus, so that one finds in primates that the three nuclei of the extrapyramidal system attain an enormous size in parts that are related phylogenetically to more recent structures. This is in contrast to the size of these nuclei in the lower mammals, even though these may have a considerably well developed cerebral and cerebellar cortex. In this connection, however, it is noteworthy that the components of this system that stand in relation to the lower levels of the brain seem to be arrested in their development. From a structural point of view this would also indicate that in the lower animals the functional status of this system (extrapyramidal) within the total motor function is entirely different from that in the primates.

Conditions are different so far as the extrapyramidal motor nuclei are concerned. The striatum, for instance, seems to represent a terminal structure which

is in no immediate connection with the cerebral cortex; this is also true of the substantia nigra. Whereas both these nuclei in the course of their development increase in size gradually, they show no such variation in structure at the expense of other parts of the brain. The corpus luysii, again, shows a different relative position in the mammalian series. As one ascends the mammalian scale its structure becomes more and more simple, resembling in this respect the periventricular gray substance of the hypothalamus. There is a possibility that in the course of this simplification of structure this nucleus may lose some of its vegetative functions and become converted into a predominatingly motor organ. Simultaneously with its structural simplification there occurs, in contrast to the hypothalamus, a relative increase in its size, which is proportional to the development of the cerebrum and the remaining extrapyramidal nuclei.

KESCHNER, New York.

ACUTE NONSUPPURATIVE INFECTIONS OF THE NERVOUS SYSTEM: CLINICAL ASPECTS. AUGUST WIMMER, Rev. neurol. **1**:193 (Feb.) 1932.

Wimmer presented this paper, which forms a companion-piece to the pathologic study by Marburg, before the general meeting of the International Neurologic Congress. Every acute infection can, under favorable circumstances, involve the nervous system. From the clinicopathologic point of view, three groups may be distinguished: the acute autonomous neurotropic disturbances; accidental, metastatic infectious encephalitis and encephalomyelitis, and intermediary forms comprising encephalomyelitis following vaccination, varicella, measles, and the idiopathic type of encephalomyelitis, which probably includes the "neuromyélite optique."

The acute autonomous infections of the nervous system comprise epidemic encephalitis, with subgroups of the para-encephalitis of Sicard, acute chorea and encephalitis of herpetic or zosterian etiology, acute anterior poliomyelitis, rabies, disseminated sclerosis and the diffuse cerebral scleroses. The metastatic encephalomyelitides occur in the course of general infectious diseases such as grip, typhoid, malaria, scarlatina, whooping cough, mumps, pneumonia and acute endocarditis. The clinical picture is dominated by the general symptoms, although the nervous phenomena may later become engrafted on it. Independent focal signs, with a tendency to regression, are more common.

In the intermediate group there are certain acute or subacute clinical pictures, the manifestations of which are highly polymorphous, and the evolution of which differs from case to case. This group comprises the acute encephalomyelitis of cryptogenic origin, that following vaccination or the well defined infections of measles and varicella. Just where epidemic hiccup and acute chorea, as well as spasmodic torticollis, should be placed is uncertain, but some of these conditions are undoubtedly related to acute epidemic encephalitis. There are reasons for believing that the virus of herpes is the same as that of epidemic encephalitis, although epidemiologically and clinically the diseases are dissimilar. The virus of herpes zoster is entirely different and would seem to be related to that of chickenpox. The lesions of zoster may be widespread in the spinal cord. Poliomyelitis is one of the best worked out of these disorders; and it is necessary to say only that there is evidence that many cases of the ascending paralysis of Landry are of poliomyelitic origin. Disseminated sclerosis is still a mystery as far as its etiology is concerned; for, although it is readily diagnosed when fully developed, its onset may be extremely varied, and the period of invasion may not be known. Acute multiple sclerosis is apparently related to the more chronic forms, but its relationship to disseminated encephalomyelitis is not yet established. Certain examples of diffuse cerebral sclerosis of Schilder's type seem to be of infectious nature, presenting histopathologic changes similar to those of multiple sclerosis or disseminated encephalomyelitis. Recent years have increased the number of cases of cryptogenic disseminated encephalomyelitis of acute or subacute character. The invasion is acute, sometimes brusk, and the symptomatology is decidedly polymorphous, with flaccid or spastic paraplegia, symptoms of combined

degeneration, acute ataxia, tremors and disorders of sphincters, sensibility and reflexes. The brain stem may be involved, with dysarthria and paralysis of the palate, and there may even be ocular disorders such as diplopia, abolition of conjugate movements and optic neuritis. The spinal fluid usually shows pleocytosis, with some increase in globulin. Irregular fever is common; delirium and somnolence are exceptional; a meningitic picture may be present. Recovery after several weeks is usual, but death may result in a few days or even hours, and there are occasional recurrences. The picture of ascending spinal paralysis may be present, and sometimes these symptoms persist. So frequently is the optic nerve involved that a special syndrome has been established, probably without justification, termed "neuromyelitis optica." The differentiation between this disorder and the onset of multiple sclerosis may be impossible, and the further history in some of these cases seems to show that multiple sclerosis was the eventual diagnosis. These disorders are not related closely to epidemic encephalitis.

Encephalomyelitis following vaccination is much like the cryptogenic disease already described, although there has apparently been no tendency to progression of the symptoms, except for one case in Winther's clinic. The nervous affections occurring in the course of measles and varicella are somewhat different, there being more meningitic signs and only occasionally those of encephalitis. It is a question whether the virus of these diseases acts directly on the nervous system or whether there is secondary invasion or chance invasion. The clinical picture is too uniform to suggest a chance invasion, yet a satisfactory means of demonstrating the virus in the brain has not yet been discovered. Finally, nobody can predicate the effect of the combined action of a neurotropic virus on a preexisting infectious disease. On the whole, the symptomatology of acute nonsuppurative encephalomyelitides is similar in all types, and the differences in the histopathology are sometimes of greater significance than those observed in the clinic.

FREEMAN, Washington, D. C.

SUMMARY OF THE PAPERS ON EPIDEMIC ENCEPHALITIS PRESENTED AT THE PARIS MEETING OF THE SOCIÉTÉS FRANÇAISES D'OTO-NEURO-OPHTHALMOLOGIE IN JUNE, 1931, Rev. d'oto-neuro-opht., November, 1931, vol. 9.

Jean-Sédan reported a case of spasm of the superogyres, in which the spasms alternated with motor crises in the lower limbs and disappeared promptly when the patient assumed a recumbent position.

Conjugate spasms of the eyes and head were discussed by D. Paulian. They follow an atypical attack of encephalitis, are rarely associated with typical parkinsonism and are late manifestations.

Worms and Chams reported two cases of associated disturbances of accommodation and convergence, one of isolated paralysis of accommodation and one of alternating paresis and contraction of the ciliary muscle. In the last, vision varied from one day to the next from myopia of 2 diopters to hyperopia of 1 diopter. The alternating spasm and relaxation of the muscle is difficult to explain, unless the cause is a modification of the muscle itself or of a hypothetic center for accommodation.

Bilateral paralysis of the third pair is the subject of an article by J. Rollet and Bujadoux. The case they reported exhibited bilateral ptosis and paralysis of all muscles supplied by the third nerves, associated with paralysis of both sides of the body. Differentiation was to be made between Parinaud's syndrome and bilateral paralysis of the third pair. They believe that if both progressive and regressive lesions were more carefully studied, central lesions of the third pair would be found more often.

The case of a child who had suffered from spasms of the head, neck and respiratory muscles for five years and who had had as many as 2,000 crises per day was reported by G. Marinesco and D. I. Vasiliu.

Velopharyngolaryngeal manifestations were discussed by F. J. Collet and J. Terracol. Collet believes that these disturbances are not of a paralytic nature,

but consist of a limitation of movement that is allied to an alteration of tonus. Terracol thinks that, in these cases, it is necessary to study all the organs concerned in phonation, respiration and deglutition. In general, the disturbances are of the type of pseudobulbar paralysis. Tremor, slow speech, deviation of the uvula and lowering of the palatine arch on one side are among the symptoms. Sensibility is usually preserved. The action of all the muscles is characterized by slowness of movement. The velopalatine reflex is variable; it is never increased.

Froment and Colrat emphasized the difficulty of ophthalmic differential diagnosis between epidemic encephalitis and multiple sclerosis. They are both characterized by lassitude, vertigo and rigidity. The type of disequilibrium is static in encephalitis and kinetic in multiple sclerosis. The only eye sign that may be considered pathognomonic is late ocular spasm, indicating encephalitis.

Labyrinthine and cochlear manifestations were discussed by George Ferreri, T. Dosuzkov, and Riser and Rigaud. Ferreri said that paracussis is the commonest complaint in the cochlear form. Of twenty patients examined by Grahe, six showed shortened bone conduction. Ferreri found slightly diminished tone perception in each of six patients examined.

Dosuzkov concluded that encephalitic parkinsonism does not show a characteristic formula of vestibular reflectivity, although when there is associated contracture of the head, there is some regularity, viz., hyporeflectivity. In cases of contracture in hyperextension or in flexion it is a matter of the liberation of the tonus of posture from the restraining influences of the vestibular apparatus, where there exists an antagonism between the reflexes of the tonus of posture and of the labyrinthine tonus. The cases of lateral deviation of the head arise from a labyrinthine tonus that is different on the two sides. According to Riser and Rigaud, the pure vestibular form of epidemic encephalitis is rare. Vestibular examination is difficult because the least movement of the patient causes painful reactions. A single examination is not sufficient to establish the bulbo-encephalitic origin of the vestibular disturbances. Syphilis may be differentiated by serologic examinations.

Dosuzkov reviewed some of the theories of muscle tonus. He has shown that, in frogs, the sympathetic ganglia take part in tonus manifestations in striated muscles. The muscle tonus of an undecerebrated and thalamic frog becomes more intense after gangliosympathectomy, but in a spinal frog the tonus is diminished by this operation. This contradictory result may exist, assuming the theory of Langley, because the individuality of the different kinds of muscle tonus is conserved after the exit of the nerve fibers from the spinal cord. Medullary tonus passes by way of the sympathetic ganglia, but cerebral tonus does not, and there is reciprocal antagonism between them.

DENNIS, Colorado Springs, Colo.

SYMPTOMATOLOGY OF FRONTAL AND TEMPOROSPHENOIDAL TUMORS. F. KENNEDY, J. A. M. A. **98**:864 (March 12) 1932.

Kennedy states that because of the paucity of definitely known, physiologic centers in the frontal lobes, the diagnosis of formation of tumor in these areas has long been difficult. Neurologists have been forced to look for main guidance to the results of pressure exerted backward on either the pyramidal tracts or their cortical origins, and to presence of change in the mental state as a confirmatory factor. Alterations in mental and emotional condition appear more frequently here than from expanding lesions elsewhere. First is seen a lessening in power of attention; irrelevant replies are made. There develops a trivial and meaningless jocosity. Short periods of excitement occur, with foolish, inept and causeless laughter. There is a tendency to take offense easily, with, on the other hand, effusive apologies over trifles. Frontal epilepsy is frequent, characterized by petit mal and sudden attacks of mental confusion. With increase in pressure, hebetude replaces these earlier manifestations; the patient lapses at times into stupor and often can be roused only with difficulty. Frontal stupor is hebephrenic and less

profound than is the morbid sleep induced by hypothalamic lesions; patients of the latter order can be roused to crystal-clear consciousness, whereas frontal stupors, by stimulation, are changed to a merely turbid or muddied awareness. There is frequent and characteristic yawning, and urinary incontinence appears earlier than would be warranted by the degree of drowsiness. Headache is less prominent than usual; possibly the lowering of mental level makes complaint less articulate. There may come forced grasping or tonic perseveration of muscular action in the contralateral hand, from involvement of the anterior part of the corpus callosum and the frontopontocerebellar fibers. In the author's experience, the only station characteristic of disease in this area is titubation on the heels, with a tendency to retropulsion. Compression backward often produces mild contralateral pyramidal tract signs, but one must remember that a meningioma placed anteriorly may press across the midline of the brain, giving rise to a similar motor reduction and to reflex changes on the same side as the main growth. Phenomena of lateralizing value in temporosphenoidal tumors consist of the perversions of contiguous functions. The motor tracts and their cortical origins may become so compressed as to give rise to a considerable degree of hemiplegia, which is always most severe in the face, less in the arm, and least of all in the leg. Deep pressure may introduce thalamic coloring: paresis of emotional expression in the opposite side of the face, and occasionally increased sensitiveness in the opposite side of the body. Rarely, athetosis may appear. The author has seen fluctuating pressure on the midbrain by a temporosphenoidal tumor produce fluctuating Argyll Robertson pupillary reactions. However, the most accurate localizing sign has been described elaborately by Harvey Cushing: a quadrantic homonymous hemianopic defect in the contralateral visual field. This occurs from involvement of Meyer's loop of temporal optic fibers; should pressure continue, the pulvinar or the main optic tract may be damaged, giving rise to a complete homonymous hemianopia. When aphasia is present, it is constant in character: a poverty of recollection of names, resulting in circumlocution and descriptive speech. There is perseveration of verbal error, with no difficulty in emission; word blindness does not occur. Almost never is there any word deafness; spoken commands are accurately performed; verbal mistakes are immediately recognized and, if possible, corrected. The power of discrimination in the value of words is proved by the fact that inaccurate promptings are invariably rejected. There is no true loss of word memory, only a dimming of word recollection. The memories are for the most part intact, but their facilitation is difficult, and the patient is unable by force of will to bring them above the threshold of consciousness, below which they lie latent and beyond the patient's conscious grasp.

EDITOR'S ABSTRACT.

THE VESTIBULAR SYNDROME. THE CEREBELLAR SYNDROME. J. A. BARRÉ, Rev. d'oto-neuro-opht. **10**:1 (Jan.) 1932.

Until recent times considered to be Siamese twins, the vestibular and cerebellar syndromes are, nevertheless, often isolated and almost always easily dissociable. Vestibular and cerebellar disturbances may coexist, but it can no longer be maintained that there is a group of symptoms common to both conditions—for example, vertigo, nystagmus and staggering.

The sign of vestibular disharmony, previously described by Barré, is of special interest in cases in which the classical cerebellar signs are not clear. Ordinarily, in a case of vestibular disorder the spontaneous nystagmus is in the direction opposite to the deviation of the arms and trunk. When a cerebellar lesion coexists, the nystagmus is toward the same side as the deviation of the arm, the body deviates to the side opposite to that to which the arms deviate, or deviation of the extended arms may be absent even though the Romberg sign is clear and there is nystagmus. The most frequent cause of vestibular disharmony is a cerebellar disturbance and this should be first thought of in the absence of a peripheral obstacle (acute otitis supervening on a chronic otorrhea) or of a pyramidal or extrapyramidal lesion. These causes of error are easily recognizable. "Cerebellar

nystagmus" and "cerebellar vertigo" have not been considered, because Barré does not believe that there exists a true vertigo or nystagmus without a concomitant vestibular disorder.

The vestibular syndrome is different from the cerebellar syndrome. While the cerebellar signs reveal either asynergia or hyposthenia, the vestibular signs always rest on disturbed tonus, which causes slow deviations of the head, eyes, limbs and trunk. The signs are not unilateral and homolateral for a unilateral lesion; they are bilateral and more marked on the side of the lesion. True vertigo, vestibular nystagmus and slow deviations are the most important signs. With the Romberg test, in vestibular disorders, the deviation of the body is toward the same side as the deviation of the arms and even slight deviations may be measured with the plumb line. It is essential to resort to vestibular tests in cases in which there is no spontaneous nystagmus, vertigo or deviation. All three tests, turning, caloric and galvanic, should be used since they give different results.

Disorders of gait are often notably different in the two syndromes. The vestibular patient may walk correctly, or he may deviate laterally while walking. With a unilateral lesion he usually does not stagger, but deviates to one side when walking forward and to the opposite side on walking backward. Confusion between cerebellar staggering and the abnormal vestibular gait is hardly possible except in cases of intense bilateral vestibular disorder. In cerebellar cases, the difficulty is due to a lack or synergy, to the absence or perturbation of the automatic liaison between the muscles of the trunk and the legs and to dysmetric movements of the segments of the limbs. In vestibular cases, the movements of the segments of the limbs and the trunk are coordinated, but there is a battle between two pulsions acting in opposite directions. The synergy is easily demonstrable in a pure vestibular case by analyzing the movements while the patient is recumbent.

Clinically, a large number of pure vestibular cases are encountered, but the number of pure cerebellar syndromes is small. Difficulty is met when the two are associated and the error to be avoided is that of attributing to one cause all the signs observed. A number of problems that still need elucidation are suggested. For their solution Barré urges a close cooperation between neurologists, ophthalmologists and otologists, after first agreeing on a uniform technic of examination.

DENNIS, Colorado Springs, Colo.

ELECTRICAL STIMULATION OF THE BASAL GANGLIA IN A CASE OF ANENCEPHALY. ROY GRINKER, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:573, 1931.

Grinker had the opportunity to study an anencephalic monster which lived for four days; he stimulated the basal ganglion region electrically. The infant had a large spina bifida in the lumbar region. It cried and yawned, made sucking movements with tongue and lips and swallowed fluids. The eyes were in divergence and deviated downward; the pupils did not react to light. Auditory reflexes, Moro's reflex and tonic neck reflexes were not present. No spontaneous movements were made by the child except for a few purposeless motions. The child could move its head when placed on its stomach. The deep reflexes were active. The face was normally developed, but the eyes were very prominent. The cranial vault was open in the parieto-occipital region, and in place of the bony calvarium there was a soft, red-brown membrane, which was covered by a skinlike membrane. When this was opened, a slightly yellow fluid escaped. No brain tissue could be seen, but a pair of protuberances were found which appeared to be the corpora striata. These were stimulated by a weak faradic current with bipolar electrodes. Stimulation of the right side produced a slow flexion of the left elbow against the abdomen. The hip, too, was flexed. At the same time the knee was slightly bent, and athetoid movements appeared in the hands and fingers. The head and neck remained absolutely quiet. All the movements ceased with cessation of the current. When the left side was stimulated, similar movements appeared on the right. Repetition of the experiment produced the same result constantly. When the most oral part of the protuberances was stimulated,

movements of the opposite arms and to a lesser degree of the legs were noted. Stimulation of the most caudal portion caused movements both of arms and of legs. Lateral stimulation caused no movements at all.

The child lived for two days after the experiments and behaved like a normal infant. It cried, slept and took nourishment from a dropper.

Microscopic study showed that the tissue mass on the surface was connective tissue. There was much inflammation in the specimen, and this interfered somewhat with the interpretation of the findings. In a few places sclerotic cortical tissue was found; it contained neither ganglion cells nor nerve fibers. Ependymal tissue was present in large quantities. The hypophysis and gasserian ganglion were identified. The spinal cord, medulla and periaqueductal region were normally developed. There were no axis-cylinders in the pyramids and pes pedunculi. The midbrain was normal. The portion that was stimulated was identified as the corpus striatum.

In higher mammals, stimulation of the corpus striatum has resulted in motor reactions only inconstantly. When positive effects have been obtained they have been attributed to aberrant pyramidal fibers passing through the caudate nucleus. The pyramidal tracts were entirely lacking in this case, and the motor reactions, namely, athetoid movements and slow flexion, can be attributed safely to the basal ganglia, that is, the corpus striatum.

ALPERS, Philadelphia.

WHAT CONSTITUTES FELLOWSHIP TRAINING IN PSYCHIATRY? SOME FUNDAMENTALS. FRANKLIN G. EBAUGH, Ment. Hyg. **15**:791 (Oct.) 1931.

Psychiatry is probably the only branch of medicine in which the demand for a trained personnel exceeds the supply. To meet this demand, the Commonwealth Fund has established fellowships at several institutions. Ebaugh outlines the training methods in use at the Colorado Psychopathic Hospital, which is designed to return to the community adequately trained psychiatrists. Selection is limited, of course, to men and women with medical degrees from class A schools; a general internship is also a prerequisite. Selection is made on the basis of a personal interview, a study of personal recommendations and an evaluation of premedical training. Ebaugh prefers men with no previous psychiatric experience, believing that such students will be burdened by no preconceived ideas; he also believes that the future of psychiatry is best served by young men, because of the stimulating enthusiasm of youth and because of the greater time such men have for study and research. The course offered by the fellowship covers a two-year period, and consists of a survey of the literature, of clinical contacts in the wards and dispensaries, of extracurricular broadening activities and of special research studies. A comprehensive bibliography is presented, listing fifty-eight books in neurology, psychology and psychiatry, and in special subjects such as epilepsy, neuropathology, forensic psychiatry, and the like. It is expected that the fellow will "complete" these books during his first six months. At the end of that time an examination is given. Ebaugh gives sample questions, such as "Outline the main facts of the organic reaction types" or "Outline the treatment of psychoneuroses," which seem to call for answers in extenso. A month by month outline of the work is also given.

To provide clinical contacts, each fellow assumes responsibilities in some ward, examining and treating about one hundred patients a year, and studying in conference the diagnostic and therapeutic measures applied to the other patients. Fellows are taught special procedures, such as encephalography, cisternal puncture and examination of the spinal fluid. Emphasis is also placed on outpatient work, which includes an active child guidance clinic, several extramural centers, a follow-up clinic and a neuropsychiatric dispensary. Opportunities for research are offered, and the study of special problems is encouraged. Stimulating contacts with other medical and surgical departments are maintained. The entire program is devised to shift emphasis from the state hospital, where psychotic patients are seen in end-stages, to the community, where they are encountered early in the period of breakdown.

DAVIDSON, Newark, N. J.

THE EFFECT OF STAB WOUNDS OF THE CORPUS STRIATUM ON THE MOLAR CONCENTRATION OF THE URINE. L. TOKAY, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:47, 1931.

The hypothalamus is an important vegetative center. In the past ten years the function of the basal ganglia as a vegetative organ has aroused great interest. Isenschmid and Krehl showed that the tuber cinereum is the chief center for the regulation of temperature. Isenschmid and Schnitzler demonstrated that slight injury of the tuber cinereum increased the regulation of temperature; on the other hand, injury of dorsally situated parts of the diencephalon produced no such effects. Spiegel, too, emphasized the importance of the tuber cinereum in the regulation of temperature. On the other hand, the corpus striatum is indispensable in maintaining a constant body temperature with variations in the temperature of the outside world. Eckhardt produced polyuria by a stab wound of the corpus mammillare, and others have produced a transitory polyuria by a wound in the same area. Molitor and Pick determined that there was a central locus controlling diuresis, and that this was inhibited by the cerebrum.

With regard to the relation of the striatum to the regulation of temperature and the excretion of water, Spiegel and Reynolds thought that the punctures of this area as in the classic experiments produced not only temperature effects, but influenced the excretion of fluids as well. They showed experimentally that after injury of the head of the striatum there followed not only fever but an increase in the amount of the urine. Polyuria followed only when there was an increase in temperature. Jungmann and Meyer found an increase in the chlorides in the urine after a wound injuring the anterior third of the funiculus teres. Brugsch, Lewy, and Dresel tried to show that the seat of the rhombencephalic centers which regulate the water content and the excretion of chloride are located in the formatio reticularis.

Tokay, extending the experiments of Spiegel and Reynolds, found that a stab wound of the head of the caudate produced not only fever but also polyuria and an increase in the chlorides in the urine. The increase in the excretion of water and chloride is most marked in the cases of increase in temperature, but it does not strictly parallel the temperature; it may be present after the fever has fallen. The increase in the excretion of chloride is often marked, even when the output of fluid is only slightly increased. Tokay concludes that in the corpus striatum are present mechanisms regulating heat, water and chloride.

ALPERS, Philadelphia.

PATHOLOGY OF THE EASTERN TYPE OF ROCKY MOUNTAIN SPOTTED FEVER. R. D. LILLIE, Pub. Health Rep. **46**:2840 (Nov. 27) 1931.

The eastern type of Rocky Mountain spotted fever occurs occasionally in the vicinity of Washington, and Lillie reports four cases that he has seen, with the results of the microscopic examination in a fifth case. The disease bears resemblances both to typhus fever and to the Montana disease, and the Weil-Felix reaction is positive. Ticks were noted in each case.

In contrast to published reports on Rocky Mountain spotted fever, the brain in the eastern type shows definite lesions, which Lillie considers under three headings, vascular and perivascular changes, focal proliferations and focal necroses. The infiltrating cells in the meninges and perivascular spaces are lymphocytes, plasma cells and macrophages. Varying degrees of necrosis of the intima and media, with hyaline thrombi and ring hemorrhages, are fairly generally disclosed. Occlusion by intimal proliferation is also observed. Compact nodules formed by proliferation of neuroglia occur both adjacent to and apart from vessels. They are composed of small round densely stained nuclei without cytoplasm, together with smaller numbers of vesicular elements and some definite rod cells. Syncytial formations are observed.

These nodules are less frequently encountered than in typhus. The site of election seems to be the inferior olives and the cerebellar cortex, but similar lesions

are found in both white and gray matter of the cerebrum. In particular contrast to typhus, Lillie finds many focal necroses in his cases. Some of these are merely areas of vacuolization in the tissues; other areas contain hyaline, pinkish material (van Gieson); in most of them the nuclei are almost completely destroyed. At a later stage the hyaline deposits undergo dissolution. Thrombosed, necrotic arterioles are seen in the centers of the lesions, with occasional extravasations, and no trace of proliferation is disclosed. These necrotic lesions occur in the white matter of the brain stem, corpus callosum and the like. Minute, basophilic, rod-shaped inclusions (rickettsiae?) were found by Lillie in the swollen endothelial cells of the thrombosed capillaries.

Lillie describes in detail the pathologic changes in other organs and compares them with the findings in typhus and Rocky Mountain spotted fever, but is guarded in drawing specific conclusions from them.

FREEMAN, Washington, D. C.

CHRONAXIA IN EPIDEMIC ENCEPHALITIS. GEORGES BOURGUIGNON, Rev. d'oto-neuro-opht. **9**:729 (Dec.) 1931.

This article is concerned with some unpublished studies on chronaxia. Vestibular chronaxia is first discussed and then chronaxia in the low forms of encephalitis. Chronaxia is defined as "a characteristic time of excitability; this time is the one that gives the threshold with an intensity (of current) twice as great as the galvanic threshold, or rheobase." Thus it is necessary to establish two thresholds in order to arrive at the excitability of a nerve.

Objects with large chronaxia are more sensitive to the action of the progressive current than objects with small chronaxia. The vestibular nerve has a very large chronaxia. When it becomes increased the rheobase diminishes, as does the threshold to the progressive current also. When it becomes diminished, the rheobase is increased, and the sensibility to the progressive current is diminished still more than the rheobase is augmented.

In postencephalitic parkinsonism the vestibular chronaxia is increased. Aside from lesions of the vestibular apparatus itself, vestibular chronaxia varies in a manner parallel to the emotivity of the patient.

There is not a specific chronaxia. Variations do not depend on the nature of the lesions or of the disease, but on the functional state of the systems in question. In epidemic encephalitis, the lesion itself is of secondary importance; the fundamental fact is the state of the function. Silent lesions, as well as symptoms that the autopsy does not appear to justify, are encountered. In order that symptoms may arise, it is only necessary that there should be a physicochemical disturbance of a certain apparatus. "The systems with the same chronaxia have the same physiologic functions and the same pathologic and physicochemical affinities." Scopolamine and eserine determine variations in attitude in the postencephalitic person by changes which they produce in the chronaxia. The state of chronaxia in encephalitis, as well as in other diseases of the nervous system, reveals with great precision the functional state of the various neurons or systems involved in the symptoms observed. Study of the vestibular chronaxia permits an approach to a study of the neurovegetative system in encephalitis. Experience has shown that it is important to study both the motor and sensory neurons for the diagnosis of central lesions.

DENNIS, Colorado Springs.

PSYCHOLOGY OF INDUCED PSYCHOSES. H. HARTMANN and E. STENGEL, Arch. f. Psychiat. **95**:584 (Nov.) 1931.

Three cases are reported in which psychoses were observed; they were those of a married couple and their daughter, aged 15. The mother, aged 41, was the first to come under observation. She was suffering from symptoms that had been gradually progressing for the past few years; they consisted of paranoid ideas. She first believed that a cousin of her husband was persecuting her.

Later, she thought that a school teacher hypnotized her daughter, and finally that people in the neighborhood were talking about her and persecuting her in other ways.

The husband and the daughter, who were primarily called in for the sake of obtaining information, showed somewhat milder but nevertheless distinct paranoid trends, which in general were in keeping with the ideas of the first patient. It appears that the psychosis started first in the woman on the basis of a certain type of personality and on the basis of difficulties in marital and economic life. The husband was sexually impotent and alcoholic; when she first began to talk to him about her suspicions of his cousin he did not agree with her, but gradually he began to believe the ideas and finally to add certain factors. The girl, who was first told of these suspicions by the mother, was herself the source of the ideas of hypnotism.

Thus, these three psychoses, although started in one person, gradually progressed by an intertwining of the different symptoms that developed in the three different persons during the course of time. Three months after their first appearance at the clinic, the wife attempted to murder the husband and daughter and to kill herself, on the basis of her paranoid ideas. Subsequent confinement in surgical and then in psychiatric hospitals resulted in clearing up in the three different persons the symptoms that were induced by the others, but certain basic symptoms, especially those that originated in the individual patient, seemed to be the most difficult to deal with. A discussion is presented of the possible mechanisms of induced psychoses in general and of those reported in particular.

MALAMUD, Iowa City.

INVESTIGATIONS INTO THE SUGAR METABOLISM IN EPILEPTIC PATIENTS, ESPECIALLY THE SUGAR THRESHOLD IN HYPERGLYCEMIA DUE TO EPINEPHRINE AND DEXTROSE. C. J. MUNCH-PETERSEN and H. I. SCHOU, Arch. psychiat. et neurol. **6**:545, 1931.

This article reports the results of an invetigation to determine whether in epileptic patients there is any difference between the sugar excretion threshold in hyperglycemia due to epinephrine and that due to dextrose. The method used was that of Hagedorn-Jensen. The results were as follows: 1. Of 166 examinations of the blood sugar in epileptic patients who were fasting 78 per cent were between 80 and 120 mg. per hundred cubic centimeters of blood, while 32 per cent were below 80 mg. There is no material difference in these results when compared with those obtained in nonepileptic persons. 2. The blood sugar curve was sometimes high and sometimes low, as in normal persons, for the same patient would sometimes show a high, and sometimes a low curve. The authors consider that the blood sugar curve after subcutaneous injection of epinephrine is without significance as to functional test. 3. The blood urine sugar threshold showed abnormal results in 33 per cent. 4. In 14 cases the same threshold after administration of epinephrine and dextrose was found in only 4 cases; the epinephrine threshold was lower in 8 cases; the dextrose threshold was lower in 1 case, and in 1 case the threshold was uncertain. In six patients the blood sugar was determined every five minutes, and the urine examined about every quarter of an hour. In three of these cases there was a lower threshold for epinephrine than for dextrose.

The total results of these investigations on the sugar threshold of epileptic patients appear to point toward a relatively frequent difference between the sugar excretion threshold after administration of epinephrine and after administration of dextrose in these patients, and toward only a small stability of their threshold functions, the latter being easily influenced by exogenous factors; perhaps it also varies spontaneously from time to time. The authors conclude that, although these findings are not peculiar to epileptic patients, they are sufficiently definite and limited to indicate a constitutionally abnormal disposition of the vegetative nervous system.

PEARSON, Philadelphia.

A Method of Ventriculography. E. M. Derry, Bull. Neurol. Inst., New York **1**:159 (June) 1931.

The author presents a standardized method of ventriculography which provides for exact observations in regard to the relative size and position of the two lateral ventricles. Ventricular estimation is dependent on the brain needle's being inserted on the two sides in an exactly similar way. Differences in the position of the two lateral ventricles with respect to a standard and to each other, as well as differences in the amounts of fluid obtained from each, constitute an important set of data which can be obtained during the operation of ventriculography. Exact measurements are made of the skull, and the standard distances used are at a point 7 cm. above the external occipital protuberance and laterally 3 cm. from the midline. The side opposite the suspected lesion is first entered; the needle is first entered straight into the brain, the shaft of the needle being at an angle of 90 degrees from the horizontal plane of the line of incision. The ventricle is encountered if it is in normal position; if not found, the needle is withdrawn to the surface, pointed laterally and reentered with the shaft forming an angle of 45 degrees with the horizontal plane. If the ventricle is not found, a third attempt is made, with the needle pointing medially, the shaft of the needle forming an angle of 135 degrees with the horizontal plane. The report is based on experience in seventy cases, in forty-five of which the standardized technic was used. In four cases, in which the conclusions based on the clinical signs and on the ventriculograms were at great variance, the additional information obtained by the use of the author's technic led to a correct localization. In four of the cases in which the ventricles failed to retain air localizing diagnosis was greatly assisted by the data obtained. The article contains excellent plates and illustrations.

Kubitschek, St. Louis.

Observations on Efficiency of Commonly Used Hypnotics. G. P. Grabfield, J. A. M. A. **96**:1865 (May 30) 1931.

Grabfield describes the observations he made in a comparison of the efficiency of commonly used hypnotic drugs. It occurred to him that a rough index of efficiency might be obtained by prescribing half the amount of the recommended doses and noting the number of doses that were required to produce a comfortable night's sleep. In this way the number of patients used, divided by the number of doses required, would give a rough index of efficiency. If the accepted dose, under such circumstances, was the correct one the indexes should run about 50 per cent. In deciding on the dose either half the pharmacopeial dose or half the dosage recommended by the manufacturer, in the case of a proprietary drug, was used. While the indexes were much higher, this method proved satisfactory. Two series of experiments were done, in the first of which a senior house officer was asked to prescribe the drug by name, and in the second one of which he was given the drug in a numbered bottle to be dispensed in the ward according to a given dosage. The drugs selected are either in the U. S. Pharmacopeia or in the accepted list of New and Nonofficial Remedies. In only one case did the newer drug show any great advantage over the older ones of the same chemical group, and that was in the case of sabromin, which has certain chemical features that differentiate it from other bromide hypnotics, but the slightly increased efficiency does not compensate for the greatly increased cost. From his observations the author concludes that chloral hydrate in small doses and barbital are the most effective and cheapest nonalkaloidal hypnotics available today. He also emphasized the fact that satisfactory results are obtained with much smaller doses than are customarily used.

Editor's Abstract.

Attacks in Postencephalitic Conditions. F. Ruecker-Embden, Arch. f. Psychiat. **93**:616, 1931.

Following a review of the literature on the different types of attack-like phenomena in postencephalitic patients, the author presents a case observed by

him. A man, aged 25, of a previously normal personality, had acute encephalitis about six years before the present communication. About three years later, a parkinsonian condition developed which was followed by the onset of the attacks. These occurred at intervals of from three days to four weeks, usually in the late afternoon or evening. They began with a dazed, somewhat hypomanic state, which was soon followed by increased activity and a press of speech. The speech then began to show perseveration and palilalia. This led up to an inability to control the production of iterations, especially of the last syllables of words. The patient then, in an attempt to stop the flow of speech, gagged himself with a handkerchief; even in this act there was an inability to cease the movement of pushing the hand into the mouth, so that there was danger of asphyxiation. The phenomena can be temporarily controlled by distracting the attention of the patient, but start again as soon as the stimulus of distraction has ceased. During the attack there is macrographia, with an increased activity of the vegetative functions, showing itself especially in increased perspiration and salivation. The parkinsonian akinesia increases after an attack.

The author advances an explanation of these states on the basis of organic disturbances which lead to an upset of the apparatus that has to do with the distribution of energy. This apparatus is one that is associated not only with motor but also with psychic and vegetative functions.

MALAMUD, Iowa City.

THE RÔLE OF THE CHOROID PLEXUS IN THE FORMATION OF THE CEREBROSPINAL FLUID. B. PURJESZ, M. DANCZ and K. HORVÁTH, Monatschr. f. Psychiat. u. Neurol. **77**:319 (Dec.) 1930.

Investigation of the changes produced in dogs by toxic substances, such as corrosive mercuric chloride, uranium nitrate and cantharides, showed that similar lesions occurred in the kidneys and choroid plexus. Poisons that affected the tubules of the kidney were apt to involve the epithelial cells of the choroid plexus. Similarly, there was a close parallelism between the alterations in the glomeruli of the former and the vascular system of the latter. An attempt was made to determine the effect of changes in the choroid plexus on the excretion of sodium iodide and lactose in the cerebrospinal fluid. Although the results obtained were not entirely satisfactory, it was found that animals treated with various poisons exhibited differences in the excretion of these substances. Lactose was also administered to several patients suffering from mental disorders, and the spinal fluid was examined at ten minute intervals for one hour and a half. In dementia paralytica and schizophrenia the amount of sugar in the spinal fluid showed little variation after this procedure, whereas in Parkinson's disease and senile dementia a rapid rise occurred. While the number of cases was small, the authors feel justified in stating that patients with different types of mental disease exhibit differences in the quantity of sugar that passes into the spinal fluid. Their experiments would seem to indicate that the formation of cerebrospinal fluid is governed by mechanisms that are analogous to those concerned in the production of urine. In their opinion, dialysis occurs through the vessels of the choroid plexus. The dialysate is then changed to a secretion by the action of the epithelial cells of the plexus.

ROTHSCHILD, Foxborough, Mass.

SOME ATYPICAL FORMS OF EPIDEMIC ENCEPHALITIS. GUNNAR KAHLMETER, Acta psychiat. et neurol. **6**:359, 1931.

Kahlmeter refers to two atypical forms of epidemic encephalitis. (1) The abortive form is characterized by fever and headache, and is often localized in the neck; there are hyperesthesia, vertigo and cranial nerve palsies. (2) The "peripheral form" shows the symptoms of polyneuritis, generally of Landry's type, and the signs of generalized infection. The majority of the cases of both types developed in the winter or the beginning of spring. Both types show an

increase of albumin in the cerebrospinal fluid, with little or no increase in the number of cells. In addition to these two atypical types, Kahlmeter points out that in recent years he has encountered a number of cases of acute diseases of the central nervous system the etiology of which seems to be an acute infection but the clinical syndromes are varied and bizarre. He reports a series of these cases. In three cases the clinical picture was that of disseminated sclerosis, and in one the autopsy showed the pathologic condition of epidemic encephalitis. In two cases, both verified at autopsy, the pathologic changes and the symptoms were localized around the bulbar nuclei and the floor of the fourth ventricle. In two cases the clinical picture was that of meningitis, although the serologic findings were practically negative. In two cases there were acute cerebral symptoms, with optic neuritis and rapid recovery. The author comments on the lack of specificity in the symptoms presented by these nine patients. Usually they would be diagnosed as acute disseminated encephalitic myelitis. Autopsies in three cases, however, revealed definite epidemic encephalitis. He wonders if all nine are not atypical cases of the same disease.

PEARSON, Philadelphia.

RECURRING BULLOUS KERATITIS, FOLLOWING, AFTER TEN YEARS, A SEROUS MENINGITIS OF THE POSTERIOR FOSSA. VILLARD AND H. ROGER, Rev. d'oto-neuro-opht. **9**:755 (Dec.) 1931.

The first stage in the evolution of the case occurred in 1918, with a syndrome of intracranial hypertension, localized in the left posterior cranial fossa, which was characterized by violent occipital headaches and vertigo, and deviation of the arm to the left. The Wassermann test of the blood and spinal fluid gave negative results. This stage lasted for about two years, but recovery was not complete. Crises of headache and vertigo occurred. Antisyphilitic treatment was without beneficial effect. In the intervals of the crises the patient complained of a sensation of heaviness and stiffness of the neck, fatigue of the arms, periods of transient obnubilation, in two of which falls from a motorcycle occurred, abnormal sensations in the left side of the face and a sensation of constriction of the left auditory meatus.

In May, 1930, recurring attacks of visual disturbances in the left eye began (the right eye was blind from previous trauma). Examination revealed a bullous keratitis and hypesthesia of the cornea, slight signs of reaction of the left trigeminal nerve, characterized by pain on pressure over the infra-orbital nerve, and hypesthesia in the domain of the ophthalmic and superior maxillary branches.

The authors believe that they are warranted in attributing the trigeminal syndrome to the primary attack of serous meningitis that has persisted through all the years and has extended lately to the region of the gasserian ganglion. The etiology remains in doubt; it appears not to be due to syphilis. The probable cause is malarial infection.

DENNIS, Colorado Springs, Colo.

FINGERTIP CAPILLARIES AND FEEBLEMINDEDNESS. M. SCHMIDTMANN, Arch. f. Psychiat. **94**:470, 1931.

The author reviews and analyzes the reports made in this field by different observers and adds a study of material of his own. The material consists of 280 mentally abnormal persons with conditions that he divides into seven groups: (1) epilepsy; (2) encephalitis; (3) psychopathy; (4) simple feeblemindedness; (5) feeblemindedness due to gross lesions of the brain; (6) mongoloid feeblemindedness, and (7) cretinism and myxedema. He finds that the most atypical forms of capillaries, that is to say, archetypes and vasoneuroses occur frequently in all the groups of feeblemindedness, especially in the last one. Intermediary forms are found regularly in all groups, and also in normal persons, and therefore cannot be designated as abnormal. The author stresses that in the literature in general the occurrence of differences of opinion and in the results of investigations of this type is probably due to differences in interpretation of the findings

rather than in the findings themselves. Frequently authors designate as one form capillaries that by other authors would be considered as being of some other form. Schmidtmann is of the opinion that atypical capillary forms are phenomena only of general psychophysical inferiority and must be considered as such and not as occurrences in themselves. He thinks that the cause of the occurrence of abnormal capillary forms must be looked for in the condition of the skin and he finds, in cases of feeblemindedness that are associated with diseases of the skin, that the capillaries differ in form in relation to the diseases of the skin.

MALAMUD, Iowa City.

BIOGENETIC INTERPRETATIONS OF CERTAIN POSTURES OF THE UPPER EXTREMITIES. G. D. LESTČENKO and L. L. ROCHLIN, Monatschr. f. Psychiat. u. Neurol. **78**:166 (Feb.) 1931.

Lestčenko and Rochlin call attention to the resemblance between certain deformities of the fingers occurring in arthritis and the postures observed in lesions of the central nervous system. Two cases of arthritis deformans are described in which there were marked flexion at the metacarpophalangeal joints, extension at the first interphalangeal joints and flexion at the joints between the middle and terminal phalanges. From a survey of the literature, the authors conclude that this type of deformity is commoner than is generally supposed. Numerous observers have regarded it as neurogenic in origin. Charcot believed that it arose from reflex irritation. On the other hand, it is known that rheumatoid infections are apt to involve the central nervous system, particularly the basal ganglia. Such involvement may lead to the emergence of lower mechanisms controlling various postures of the fingers. Lestčenko and Rochlin are of the opinion that this plays an important part in the origin of the deformities that occurred in their cases. The arthritic process develops simultaneously with the central lesion, causing a fixation and exaggeration of the posture in question. In support of this view, they report a third case in which the same type of deformity, combined with athetoid movements, was produced by a cerebral lesion following typhus fever. A study of the fingers of apes does not reveal anything similar to the position of the hand observed by them. Hence from a biogenetic standpoint it must be looked on as an archaic posture that can be traced to a very primitive stage of phylogenetic development.

ROTHSCHILD, Foxborough, Mass.

RETROGRADE DEGENERATION IN THE LATERAL HORNS OF MAN AFTER ANTERIOR ROOT TRANSECTION. O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:565, 1931.

On the basis of previous experiments on apes, investigators have concluded that the lateral horns are spinal vegetative centers. This has been substantiated by anatomic studies. It has been assumed furthermore that the fibers from these centers pass out through the anterior roots; if this is so, transection of the latter should be followed by retrograde degeneration in the lateral horn cells.

Gagel studied a case in which there was transection of the anterior roots followed by death in eight days. The patient suffered severe pain in the cauda equinal distribution as a result of a metastatic growth. Foerster cut the third and fourth thoracic anterior and posterior roots. Microscopic examination showed the anterior horn cells to be pale, their Nissl granules washed out and often a shrunken and eccentric nucleus. In other levels, the lateral horn cells were decreased in number. The cells of the lateral horns showed, therefore, a typical retrograde degeneration. These observations speak for the fact that the nerve fibers from the lateral horns pass through the anterior roots. The objection may be raised that the lateral horn changes in this case may have been due to section of the posterior root. A similar case in which the patient was operated on by Foerster, in which only the posterior roots were cut, showed no pathologic changes whatever

in the lateral horns, whereas there were changes to be noted in the anterior horns, in Clarke's column and in the intermediate column of cells.

The nerve fibers from the lateral horns pass out through the anterior roots to the sympathetic chain.

ALPERS, Philadelphia.

THE FUNCTION AND ACTION OF THE CEREBROSPINAL FLUID. FEDELE NEGRO, Rev. neurol. **2**:790 (Dec.) 1931.

In a case presenting a fistula after removal of a spinal tumor, the patient died twenty days after operation in a state of extreme cachexia. This led the author to perform experiments in which he found that loss of cerebrospinal fluid was followed by apathy, somnolence, hypothermia, muscular asthenia, slowing of the pulse and respiration, falling of the hair and rapid wasting, with death in from ten to fifteen days. Pathologic examination revealed extremely marked atrophy of all the organs.

Animals given injections of cerebrospinal fluid showed more rapid growth, an increase in the amount of hair and earlier maturity. When patients were given from 20 to 30 daily injections of 20 cc., many changes were observed, such as increased blood pressure, basal metabolism, hemoglobin and weight, improvement in physical and intellectual functions, increased sexual activity and some restoration of sexual power. In women, dysfunction of the ovary was corrected and the nervous disturbances of the menopause improved remarkably. Improvement was specific in cases of diabetes insipidus. This leads the author to state positively that the cerebrospinal fluid has a regulating influence on the metabolism of tissues and is of definite clinical usefulness.

FREEMAN, Washington, D. C.

AN EPIDEMIC OF POLYNEURITIS OF PECULIAR ORIGIN. J. W. G. TER BRAACK, Nederl. tijdschr. v. geneesk. **75**:2329 (May 2) 1931.

Ten cases of polyneuritis in pregnant women are described by the author in which the symptoms were essentially symmetrical paralysis of distal muscle groups without any objective disturbance of sensibility. The patellar reflexes were retained, but the achilles jerks were absent. In nine of the cases some dark colored cathartic had been consumed from ten to twenty days previously. Electrical testing of the muscles showed partial and total reactions of degeneration of the small muscles of the hands as well as of the feet. The opponens pollicis was affected early and strikingly. At the onset of the illness, vomiting, diarrhea and abdominal pain were complained of. One woman had an abortion. From two to three weeks after these symptoms, paresthesia and paralysis developed in the feet and later in the hands. A reducing substance was found in the urine. The atrophy was not pronounced. The loss of electrical response suggested a prolonged recovery. One of the women had used a French cathartic called "apiol," which contained phenolates and an ethereal extract of petersilien seeds. The poisonous nature of this material is well known. Whether the extract of petersilien alone or the mixture of the ingredients in the cathartic was responsible remains unsettled.

HART, Greenwich, Conn.

SUBACUTE MENINGOCOCCAL ENDOCARDITIS. NORMAN B. GWYN, Arch. Int. Med. **48**: 1110 (Dec.) 1931.

Meningococcic endocarditis without meningitis has been known since 1903; meningococcic endocarditis with meningeal involvement is even better known. Gwyn's patient was a woman, aged 37, who had complained of headache and pain in the chest for eight months. As a result of the persistence of fever, enlarged heart and a systolic mitral murmur, as well as petechiae and albuminuria, a diagnosis of subacute bacterial endocarditis had been made. On three occasions the patient had short attacks of unconsciousness, presumably due to cerebral embolism. She was admitted to the hospital with signs of meningitis.

Cultures of both blood and spinal fluid showed meningococci; the leukocyte count was low, never exceeding 12,000. The patient gave evidence of increase of intracranial pressure with a distinct papilledema. At autopsy, enlargement of the heart, spleen, kidneys and liver was found. The mitral valve showed destructive ulcerations, cultures from which were sterile. The kidneys revealed both glomerular and interstitial nephritis. The brain and spinal cord were diffusely inflamed, and from the exudate of these tissues meningococci were readily cultivated. Gwyn believes that one should consider more ofter the possibility of chronic septicemia being due to meningococcic invasion.

DAVIDSON, Newark, N. J.

THE EFFECT OF ALCOHOL ON THE NERVE CELLS OF RATS. R. T. YOUNG, J. Comp. Neurol. **52**:22 (Feb.) 1931.

Rats were placed in alcoholic fumes until they were unable to stand. They were then removed and allowed to recover. This was done daily for periods varying from twenty to thirty-two days, or in two periods of thirty days each with a thirty-day interval. Most of the animals were killed before recovery, and the brains and spinal cords were rapidly removed and fixed in various fixing solutions. The nerve cells selected were the anterior horn cells of the spinal cord, the Purkinje cells of the cerebellar cortex and the pyramidal cells of the cerebral cortex. The size of the cells alone showed change after this treatment. The cytoplasm was more affected than the nucleus and thereby the N/P (nucleo-plasma) ratio was increased. The author believes this to be due to the extraction of water from the cells. There was greater variability in the cells of the control than in those of the treated animals. In the motor cells the author suggests this may be due to the greater activity in the control animal. The author believes that the changes produced by alcohol as described by other investigators may be artefacts due to postmortem changes, imperfect fixation or differential staining.

ADDISON, Philadelphia.

GRANULES IN NEUTROPHILIC LEUKOCYTES IN MENTAL DISEASES. D. I. EFFREMOFF, J. nevropat. i psikhiat. **7**:68, 1931.

The author reviews the literature on hematology, which shows that the presence of large granules in neutrophils means the presence of toxins in the organism. One hundred and thirty-five patients were studied, and as a control, a group of fifteen patients who had recovered were checked. Blood films were prepared according to Freifeldt's method (methylene blue and carbolfuchsin) in sixty-six cases of schizophrenia. Granulations and definite changes in the protoplasm were found in 86 per cent of the cases. All cases of chronic tuberculosis were excluded from this group. Only one half of twenty-five patients with dementia paralytica showed the presence of granulations. The granulations were present more frequently in the acute stages than in the chronic. Only two of fifteen patients who recovered from schizophrenia showed the presence of granulations. The disappearance of the large granules from the white cells is parallel with the improvement in the general condition of the patient. In the chronic cases the degenerative processes in the protoplasm were more common than the granulations. The author believes that the blood picture in schizophrenia suggests that there are toxic factors that are probably responsible for the disease.

KASANIN, Howard, R. I.

THE DEVELOPMENT OF THE BRAIN OF BDELLOSTOMA STOUTI. INTERNAL GROWTH CHANGES. J. LEROY CONEL, J. Comp. Neurol. **52**:365 (June) 1931.

This study shows that the embryonic brain of myxinoids has a generalized structure similar to that of the brain of Necturus. On the basis of development the author believes the myxinoids primitive rather than degenerate, except in the case of the eye. The eye has degenerated, resulting in a corresponding atrophy

in the mesencephalon. In young embryos the ventricles are coextensive with the wall of the brain. As shown in the illustrations, the lateral ventricles disappear first and the median probably next. The presence of the cerebellum is doubtful. In the telencephalon, the olfactory bulb, primordium hippocampi, area basalis and hemispheres can be identified and followed in development. In the youngest embryos the hemispheres are well advanced. The diencephalon shows: epiphysis, habenula, pars intercalaris diencephali, eminentia thalami, thalamus, hypothalamus, infundibulum and mammillary bodies. The reduced mesencephalon is shaped like an inverted pyramid and shows tectum, tegmentum and posterior tubercle. The rhombencephalon shows an eminentia subcerebellaris and lobi auriculares. The auricular lobes grow in relation to the development of the trigeminal nerve.

ADDISON, Philadelphia.

A CASE OF DERMOID OVERLYING THE CEREBELLAR VERMIS. SAMUEL BROCK and D. A. KLENKE, Bull. Neurol. Inst., New York **1**:159 (June) 1931.

The authors report in detail a case of calcified dermoid which consisted of irregular pieces of tissue, from soft to cartilaginous and bony in consistency, and many strands of matted hair. Microscopically, the chief elements were thick, fibrous connective tissue, containing small masses of cartilage, bone and rudimentary hair follicles. Localizing diagnosis presented some difficulty, owing to the occurrence of uncinate fits which led the examiner to suspect a growth in the right temporal lobe. However, roentgenograms showed small areas of calcification in the midline in the posterior fossa. Roentgenologists considered the lesion might be an ependymoma. Ventriculography, which showed symmetrical dilation of both lateral ventricles, of the third ventricle and of the aqueduct of Sylvius up to the area of calcification, was of decided diagnostic assistance. The authors review the literature on the subject and have summarized reports of intracranial dermoids that have been published.

KUBITSCHEK, St. Louis.

CONTRIBUTION TO THE STUDY OF THE PSYCHOLOGY OF THE JEW. D. WOLBERG-SOBOLÉVIC, Progrès méd., Sept. 12, 1931, p. 1584.

The psychologic differences between Jews and non-Jews were investigated among college students, and in scholars of both upper and lower classes. Visual imagination, the capacity for observation of visual memories and the capacity of combination were tested. It still remains questionable to what extent up-bringing and environmental influence were of importance in the children studied. The geographic dissemination of Jews and their establishment in many lands, the varied social and economic relationships, the manifold traditions and superstitions and the customs and influences of the surrounding peoples can produce fundamental errors in such a psychologic investigation. The non-Jews showed similar results, which differed only slightly in the older subjects. The critical faculty in Jewish children seems to be definitely more developed; they seemed often to be more mature than the others, although in visual function they were found inferior.

HART, Greenwich, Conn.

THE ROENTGENOTHERAPY OF PITUITARY TUMORS. C. G. DYKE and S. W. GROSS, Bull. Neurol. Inst., New York **1**:159 (June) 1931.

The authors present studies of the case histories of five patients in which a diagnosis of pituitary tumor had been made, who were treated by roentgenotherapy. In all the patients headache was entirely relieved following roentgenotherapy; three patients showed marked improvement in visual fields and visual acuity; two patients lost considerable weight; two patients showed no improvement of vision, but there was no further loss of vision, and subjectively they seemed somewhat improved. The authors express the opinion that roentgenotherapy must

be prolonged and vigorous and that treatment must be continued even though favorable results are obtained after the first series of treatments. The importance of charting visual fields and acuity after every roentgen treatment is emphasized as the best guide to the patient's reaction.

KUBITSCHEK, St. Louis.

THE INCIDENCE OF PARENCHYMATOUS KERATITIS IN HERPES ZOSTER OPHTHALMICUS. A NEW CASE OF ARGYLL ROBERTSON PUPIL AS A UNILATERAL SIGN FOLLOWING HERPES ZOSTER OPHTHALMICUS. V. VALIÈRE-VIALEIX, Ann. d'ocul. **168**:341 (May) 1931.

Valière-Vialeix reports a case of typical unilateral Argyll Robertson pupil discovered after cure of herpes zoster ophthalmicus complicated by parenchymatous keratitis and iridocyclitis with increased intra-ocular pressure. The presence of Argyll Robertson pupil complicating herpes zoster of the fifth nerve is exceedingly rare and has been doubted by some authors, owing to the fact that the patients were not examined before the onset of herpes. In the case reported by Valière-Vialeix, a careful examination of the iris was made at the onset of the disease, and no disturbance of the reflexes was noted. The author is inclined to believe that the Argyll Robertson pupil is due to ciliary perineuritis which Meller, in 1920, demonstrated as important.

THERAPY OF TUMORS OF THE HYPOPHYSIS. V. MAZAL, Ann. d'ocul. **168**:941 (Nov.) 1931.

Mazal states that tumors of the hypophysis are treated by operation, by roentgen therapy or, rarely, by opotherapy. Of twenty-three patients at the ophthalmologic clinic in Brno, eighteen were treated with roentgen rays with the following results: twelve were improved, two were unimproved, and in four the condition was aggravated (later two were slightly improved). Two patients had to be operated on. The condition was improved in one of these cases and in the other the vision diminished. Although the majority of cases reacted favorably to roentgen therapy and this method may be harmless in the hands of a trained specialist, cystic tumors and growths classified as malignant tumors which lead to rapid diminution of visual acuity and symptoms pointing to increased intracranial pressure should be operated on.

TWO CASES OF LINDAU'S DISEASE: ANGIOMA OF THE CEREBELLUM IN THE MOTHER AND VON HIPPEL'S DISEASE IN THE SON. E. HARTMANN and G. SOURDILLE, Ann. d'ocul. **168**:881 (Nov.) 1931.

Cases of angioma of the cerebellum in a mother associated with Lindau's disease and of angiomatosis retinae (von Hippel's disease) in her son are reported by Hartmann and Sourdille. The authors point to the association of these two diseases, which are often found in the same patient, as further evidence of the close relation between the brain and the eye which is evident from anatomic, histologic and embryologic studies. They believe that these cases point to the familial character of Lindau's disease and urge careful examination of the periphery of the fundus in patients who are suspected of having cerebral tumors.

BERENS, New York.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Annual Meeting, May 28, 1932

SIDNEY D. WILGUS, M.D., *President, in the Chair*

EFFECT OF EPHEDRINE HYDROCHLORIDE ON BLOOD SUGAR MOBILIZATION IN CHRONIC ENCEPHALITIS. DR. ISIDORE FINKELMAN (by invitation).

Ephedrine hydrochloride was used as a sympathicomimetic drug to observe its effect on blood sugar mobilization in chronic encephalitis. Seven of the fourteen curves for blood sugar obtained in chronic encephalitis showed a reversal of the ephedrine action. In the other seven, the levels for blood sugar, although not reversed, were not as high as those of the eight control subjects. This failure of blood sugar mobilization after stimulation with ephedrine in chronic encephalitis may be due to lesions involving to a greater or lesser extent central sympathetic nuclei. The level for blood sugar was raised after the injection of ephedrine in patients treated with parasympathetic depressants. This confirms the evidence of the existence of parasympathetic predominance in chronic encephalitis. It also speaks against the presence of local changes in the liver in this disease.

A COMPARISON OF THE TAKATA-ARA, GUM MASTIC AND COLLOIDAL GOLD REACTIONS OF SPINAL FLUID. MR. DE LESTER SACKETT, DR. WILLIAM B. QUANTZ and MR. ERIC ESELIUS (by invitation).

The sublimate-fuchsin reaction of Maki Takata and Kiyoshi Ara was devised in 1925. Monias' modification of this test is: A solution of mercuric chloride is mixed with a solution of sodium hydroxide in the presence of spinal fluid, forming a colloidal solution of mercuric oxide which is turned a deep bluish violet by the addition of a solution of diamond-fuchsin. An abnormal protein content of the fluid causes either a flocculation of the mercuric oxide with discoloration of the fluid in syphilis, or color changes from bluish violet to pink with practically no flocculation in bacterial meningitis. The gum mastic colloidal reaction depends on the precipitation of the gum in the presence of abnormal fluid.

In 160 cases of dementia paralytica (cerebral type) we found 94.3 per cent positive reactions with the Lange test, 83.1 per cent with the mastic and 85.6 per cent with the Takata-Ara test. In 29 cases of dementia paralytica (tabetic type) the Lange test was positive in 90.7 per cent, the mastic test in 82.8 per cent and the Takata-Ara test in 86.1 per cent. In 10 cases of cerebrospinal syphilis all tests gave 70 per cent positive reactions. There was not a uniform curve in any type of reaction that was typical for any of the three conditions, for similar curves were found in all three types of the disease.

From these results it would seem that the value of the three reactions ranges in the following order: Lange, Takata-Ara and gum mastic. However, this conclusion does not follow when one considers the negative controls. Seventy-six fluids, with negative Wassermann reactions, from 41 cases of dementia praecox, 8 of cerebral arteriosclerosis, 1 of mental deficiency, 5 of manic-depressive psychosis, 3 of epilepsy, 1 of psychopathic personality, 7 of chronic alcoholism, 1 of traumatic psychosis, 4 of no psychosis, 1 of postencephalitis, 1 of senile dementia, 2 of involution melancholia and 1 of psychosis with cerebral or nervous disease were used. The Lange test gave 17.1 per cent positive reactions, the mastic 1.3 per cent and the Takata-Ara test 22.3 per cent. These results, however, are misleading, as the positive Lange tests did not contain any tube with a 2 plus reaction; this

would not be considered a grave error, for no positive conclusions could be reached from this type of reaction. The positive mastic reactions were likewise weak and would not be confused with positive conclusions. The positive Takata-Ara reactions, however, contained 76.4 per cent among the false positive reactions that were greater than 2 plus, and 11.7 per cent of these were even 5 plus reactions. It is interesting that the 5 plus reactions occurred in cases of cerebral arteriosclerosis.

In 4 cases of bacterial meningitis the Takata-Ara test gave the color reactions typical for this infection, while the Lange and mastic tests gave indefinite reactions which would not help to distinguish the condition from a syphilitic infection.

A Case of Paget's Disease (Osteitis Deformans). Dr. Maurice A. Schiller (by invitation).

Mrs. A. C., a white woman, aged 60, was admitted for the second time to the Elgin State Hospital on Oct. 9, 1931. She had had articular rheumatism at 17, typhoid fever at 18, and an appendectomy and right inguinal herniotomy at 45 years of age. At her first admission to the hospital in 1907, she was nervous, suffered from insomnia, and thought that everything in the house was crooked and not as it used to be. She was depressed, cried and showed some fear reaction. She was neat and tidy in habits, and helped with the work about the hospital. Physical examination gave essentially negative results; there were no deformities.

She was paroled five times, but adjusted herself poorly because the false ideas persisted. She was discharged as improved on June 22, 1912. Following discharge, she adjusted herself to her environment fairly well, worked as a cashier for two years and married. She was divorced and about one year prior to the second admission to the hospital married a man twenty years her junior after having known him for only three weeks.

She passed through the menopause at the age of 50, and since has noticed a slow, gradual increase in the size of the head. The arms and legs became wider and bowed. At no time did she have any headaches or pain in connection with the deformities. In September, 1931, she became restless, insomnia developed, and she thought that needles were pricking her and that her room was filled with gas. She imagined that her clothes were in rags and that she would be shot.

Physical Examination.—The patient was well nourished, was 5 feet, 1½ inches (156.2 cm.) in height, and weighed 135 pounds (61.2 Kg.). The mandible was thickened, enlarged and somewhat protruding. The cranium was enlarged; it measured: circumference, 57 cm.; fronto-occipital diameter, 19.4 cm.; biparietal diameter, 15.6 cm.; mento-occipital diameter, 25.4 cm.; bitemporal diameter 14.8 cm. There were also thickening and anterior bowing of both tibias (most marked on the right), and thickening and dorsal bowing of both ulnas (most marked on the left). Except for bilateral hallux valgus, there were no other deformities. The teeth were absent; the throat was normal; the thyroid gland was slightly palpable. The heart and lungs were normal. The pulse was 80 in rate and regular and fairly compressible. The blood pressure was 120 systolic and 72 diastolic. The abdomen was normal except for appendectomy and right herniotomy scars. There were no genito-urinary abnormalities, and neurologic examination gave entirely negative results. Ophthalmoscopic examination revealed an increase in the diameter of the retinal veins, with narrowing and beginning sclerosis of the retinal arteries.

Roentgen examination of the osseous system revealed extensive Paget's disease of the skull, and of both upper and lower extremities.

Laboratory Examinations.—The urine was normal, and the Wassermann and Kahn tests of the blood were negative. The blood calcium was 12.3 mg. and phosphorus 3.27 mg. per hundred cubic centimeters.

Mental Examination.—The patient was quiet, cooperative and well oriented. Recent memory was good and remote memory was fair. Retention and general information were fair but calculation was very poor. Judgment was fair accord-

ing to the usual test stories. At the time of examination she had insight into her condition, recognized her delusions as imaginary ideas and said that she was melancholy because her husband was out of work.

Since admission, she has had periods of confusion lasting for several days at a time when she is disoriented, loses herself in the ward and becomes somewhat agitated and depressed. She has lucid intervals between these clouded periods. The mental condition at this time is evidently on the basis of a cerebral arteriosclerosis.

A Study of the Effect of Fever Therapy on the Permeability Quotient in Dementia Paralytica. Dr. Sidney D. Wilgus, Dr. William B. Quantz and Dr. Ralph H. Kuhns.

The Walter bromide test is referred to as a permeability test, or, by some authors, as a meningeal permeability test, the quotient obtained being spoken of as the permeability quotient. The details of this test are described.

We have studied 150 patients with dementia paralytica treated for two years by fever produced artificially by diathermy and an electrically heated blanket. In 80, or 54 per cent, the permeability quotient was increased; in 45, or 30 per cent, the permeability quotient remained stationary; in 25, or 16 per cent, the permeability quotient was decreased. According to the clinical records, 75, or 50 per cent, showed improvement; 30, or 20 per cent, were unimproved, and 25, or 16 per cent, were worse. No information was obtained in answer to letters concerning 20 discharged or paroled patients, 14 per cent of the total. Assuming that these patients had improved, the percentage of improvement would be 64. The results of the clinical condition of the patients corresponded, therefore, closely to the permeability quotients as determined in the laboratory.

Book Reviews

Psychological Factors in Peripheral Vision. By G. C. Grindley. Special Report Series, No. 163. Price, 1 shilling. Pp. 48. London: His Majesty's Stationery Office, 1932.

The Committee on the Physiology of Vision of the Medical Research Council has now published nine reports, of which this is the latest. Of the former reports, one was concerned with peripheral vision. (A list of these reports is given at the end of this review.) The present report contains a further contribution to this same subject, i. e., a perception of complex figures coming into view at the edges of the field of sight, the influence of the time of exposure on the accuracy of this peripheral perception of form, the influence on peripheral perception of directing voluntary attention to parts of the visual fields and the visual judgment of the position of an object lying at the periphery.

The pamphlet is divided into seven parts and a summary. In the introduction, the differences between direct and indirect vision and the various physical, retinal and central factors connected with direct and indirect vision are discussed. In the section under physical factors connected with peripheral vision, the author calls special attention to the distortion of objects which occurs in the periphery of the retina, and hence in the eccentric angle of vision, and to the fact that this distortion must be much greater when the pupil is dilated than when contracted. The aim of these experiments is outlined in the introduction to the review.

Part 2 discusses the apparatus. This was a large perimetric screen with a luminous fixation point so arranged that the eye being tested could be closely observed by the experimenter and the course of fixation checked. Eye movements of even 4 degrees could be determined with certainty. Movements greater than this were rare, and when they did occur the results were omitted. By means of a photographic shutter and a mirror the figures could be shown for any desired time on the white screen. The illumination on the screen was approximately 6 meter candles. There was one inevitable error in this experiment, in that the images at 40 and 60 degrees were slightly different from those at the 20 and 80 degree positions. This matter of equality of brightness, however, was not required in the experiments in which this apparatus was used; hence it is of no concern.

Section 3 deals with the qualitative observations on peripheral form perception. In this subject four stages in the observer's perception could be worked out: the figureless field, in which no form was seen; a formless figure, in which the form is seen first as a spot and later as an unorganized mass, and a formlike figure, in which some of the salient features of the form are seen, while others may be missed or displaced. At this stage the observers suggest tentative names for the form, and it is interesting to note that the appearance of the form may change with changes in the interpretation given to it by the observer. The fourth stage was that of a clear figure, in which the form was correctly seen.

The literature in this section on peripheral form perception is abstracted in great detail, extending over a period of many years; for instance, the early work of Hueck (1840) is included. He apparently first called attention to the decrease that occurs in visual acuity when passing from the fovea to the extreme periphery.

In the physical conditions considered with the experiments it was found that figures could be seen correctly if they were shown close to the fixation mark, though a view of the more complex figures required an exposure of more than one-tenth second for careful examination. Further, a peripheral form was more accurately seen if exposed alone on a dark field than if other forms were exposed with it.

Changes appeared in the appearance of a figure, with changes in the eccentric angle and the blur of the peripheral figure, as is to be expected from the imperfections of the image due to the extreme angle of incidence, the interconnections in the ganglion cell layer and the sparsity of receptors in the periphery of the retina. It is interesting to know that the effect of these physical and retinal factors is not immediately counteracted by central compensating factors. There is, however, a later and psychologic compensation which often occurs, so that the observer, although he may see the figure as a blurred and dim triangle, judges that it is really a triangle which is neither blurred nor dim. Compensation of this conscious kind affects the observer's final judgment but not his initial perception, and the extent to which the observer makes his final judgment different from his initial perception will, of course, depend on his preconceived idea of the kind of figure the experimenter is likely to expose. It is possible that with practice there would be a greater amount of immediate compensation, so that figures would be clearer initially, and the rather rare cases in these experiments in which the observer reported a figure far out in the periphery correctly, and described it as "quite clear," may be due to immediate compensation of this kind. The dimness of figures in the periphery is probably due to partial dark adaptation because of the brightness and size of the fixation window. The cause of the apparent smallness of figures in the extreme periphery is doubtful. There are several conflicting theories and at least one paradoxical theory; the author quotes Parson's, however: "The most probable reason is that this is due to the sparsity, of receptors in the periphery of the retina, and hence analogous to the apparent decrease in the distance between two compass points as they are moved up the arm"—a satisfactory analogy but not an explanation.

Some of the more common errors reported in peripheral form perception are as follows: (*a*) the figure reported having no recognizable relation to the figure shown; (*b*) part of the figure reported correctly; (*c*) parts of the figure reported correctly, but in an incorrect arrangement, and (*d*) changes in illumination or in brightness and apparent movements which could be grouped under illusory movements. Past experiences, expectations, as continued reporting of the same figure, various conscious processes in peripheral perception, as warnings, boredom and unconscious interpretation of a form rather than flash visual identification must also have modified results, though the degree of this is unexplainable. In this study of observations, the variability of the results was interesting. Thus, for the same complex figure, shown among a number of other figures, an observer, on different occasions, might report the figure accurately, might report it as a mere blur and might report it in ways showing most of the common errors already described. Sometimes the variations in the report could be explained by changes in the observer's mental attitude before the exposure, but more often the variations were unexplained. The variability of the reports would, no doubt, have been less if the figures had usually been shown either so close to the fixation mark as to make them clear, or so far out in the periphery as to make them merely formless blurs. It should be noted that it was in the region immediately preceding that in which the form is seen clearly, the region of "formlike figure."

Other observers found striking variations in the appearance of a form moved slowly inward from the periphery. The observers in the present experiments differed from each other in their peripheral visual acuities, in their susceptibility to illusory movements and in their susceptibility to an illusion of position. There seemed also to be differences in their cautiousness in interpreting figures that had not been seen clearly, and in their susceptibility to the erroneous rearrangement of the parts of a complex figure. One observer differed from the others in that he seldom remembered what he had seen in visual terms. The number of observers was not large enough to make it possible to infer any correlations between these individual differences.

Section 4 discusses the effect of the time of exposure. In the attempt to draw conclusions relative to the relationship of the time of exposure to peripheral vision, two series of readings were taken. In the first series a line 3½ inches (8.87 cm.) long and ¼ inch (0.64 cm.) wide, exposed at an eccentric angle of 80 degrees,

was used as a test object. The line could be in any of four orientations—horizontal, vertical or at an angle of 45 degrees to the vertical on either side—and the length of exposure could be varied from one-hundredth second to one second by means of the Compur shutter. In the second series the same line was used as a test object, but three circles, of radii ½, 1 and 1½ inches (1.27, 2.5 and 3.77 cm.), were exposed simultaneously with the line at eccentric angles of 20, 40 and 60 degrees, respectively. The line was again shown at an eccentric angle of 80 degrees.

In both series the observers were told beforehand what objects were going to appear, and they were allowed to familiarize themselves with the positions of the circles and the line by direct vision; however, they were not told beforehand the orientation in which the line was going to appear. The observers were asked to report the orientation of the line and their conscious processes as fully as possible. Readings were taken with exposures of one-hundredth, one-twenty-fifth, one-fifth and one second in each series, the long exposures being taken first on some days and the short ones on others. Equal numbers of readings with each orientation were taken at each time of exposure.

The results obtained from this showed without doubt that the course of perception increased with the time of exposure up to one second, and that below one second the course was greater when a single line was exposed alone than when a single line was exposed with circles about it.

Section 5 discusses the influence of attention. The earlier part of the work seemed to suggest that the direction of voluntary attention to a particular point in the peripheral visual field increases the accuracy of perception at that point. James, in 1895, and Helmholtz, in 1866, first discussed this. Both of these observers are quoted verbatim (James, W.: Principles of Psychology, New York, The Macmillan Company, 1895, p. 230. Helmholtz, H. L.: Handbuch der physiologischen Optik, Leipzig, L. Voss, 1867, vol. 2, p. 455). "It is not all certain that this view is correct." At all events, Dr. Grindley does not consider it of tremendous importance.

In some preliminary qualitative observations a number of subjects—all trained psychologists—were asked to fixate an object in a well illuminated room and to direct their attention successively to other objects without moving their eyes. The subjects all agreed that the objects attended to became "clearer" or "more vivid" than they had been, but they all thought it doubtful whether the objects also became "brighter" or "more intense."

The reason why attention to a particular position should facilitate the perception of an object appearing there is debatable. It is unlikely that this facilitation is produced through any change in the dioptric mechanism of the eye. Therefore, one can either suppose in accordance with the speculative theory of Henning (1925) that attention is a centrally initiated process which somehow produces sensitization of the appropriate portion of the retina or of the pathway from the eye to the cortex, or of both; or one can suppose, in accordance with the classic view of attention, that the effect is purely cortical. In any case the experiments do not show whether the effect consists of the reenforcement of response to one part of the field or of the inhibition of response to other parts, or whether it is a combination of these. All that the experiments establish is that response to one part of the field becomes relatively easier and more accurate than response to another part. While this is clearly a case in which it is not possible at present to describe the central processes involved with any certainty, it is interesting to note how well all the experimental data and introspective reports accord with William James' rather vague theory of the subexcitement of the appropriate cortical centers in sensorial attention.

In section 6, Grindley discusses the factors that play a rôle in regard to the position of a peripheral object. In this the observers were allowed to familiarize themselves with the position of a figure on the screen by direct vision, and later were shown the same figure peripherally. In several cases the observers remarked that the figures, when seen peripherally, appeared to be closer to the point of fixation than they had expected. This and the cases in which the observer saw the parts of a complex object correctly, but reported their relative positions wrongly, suggested that it would be worth while to determine the accuracy with

which an observer could determine the position of a peripheral object. It was discovered, under the conditions of the experiment, that objects which appeared for a short time in the periphery of the visual field were, on the average, judged to be at a smaller eccentric angle than their true position. Several explanations are discussed. They are just mentioned here. First, this may be similar to cutaneous localization in that, if a point on an observer's arm is stimulated and he is asked to indicate its position, he is likely to point to a position nearer to the hand, a supposition probably due to the gradual decrease in discriminative power in passing up the arm, which causes distances near the extremity to seem greater than equal distances farther up the arm. In this explanation, not advanced by Grindley, but considered by Peterson in 1926, Grindley emphasizes the apparent importance of it in that, as he states, "why the apparent magnification of distances at areas of high sensitivity as compared with distances at areas of lower sensitivity, should lead to an apparent displacement of an object towards an area of higher sensitivity is not at all clear." One might, in fact, expect that the effect would be in the opposite direction. Another explanation is based on the work of Head, in that there is a general tendency to refer stimulation from an area of low sensitivity to an area of higher sensitivity supplied by adjacent nerve fibers. Another possibility is that a momentary stimulus, such as the square in these experiments, may produce a different ratio of excitation in the rod and cone mechanisms from that produced by a stimulus of longer duration, such as a line, in that the result may be due to a hypothetical difference between sensations due to stimulation of the rods and sensations due to stimulation of the cones of the same part of the retina. A last possibility is that the illusion may be due in some way to a tendency to make eye movements. This, also, if it is to be considered, must have further work done experimentally to confirm it. Grindley's results so far obtained are not sufficient to decide which theory, if any, is true.

Section 7 consists of a general discussion of the comparison of direct and indirect vision and the significance of the results obtained. As a comparison, the perception of any given object becomes progressively less likely to be accurate as the distance of the form from the direct line of vision is increased, and it is clear that the difficulty of accurate perception at large eccentric angles is largely due to certain definite physical and retinal factors which are different in direct and in indirect vision. What differences, if any, there are between the central factors operating in direct and indirect vision are more difficult to determine. It is not possible to argue that because a given form, seen indirectly, gives rise to a certain illusion of central origin which is absent when the same form is seen directly, the central factors responsible for the illusion are peculiar to indirect vision, since it is clear that the sense data on which the central factors have to work are different in the two cases. If sense data of the same kind could be produced in direct vision, the same kind of illusion might occur. It would, of course, be possible to compare the perception of a number of forms seen indirectly with that of a number of similar forms in direct vision, the difficulty of perception (as measured by the number of right answers) being made equal in the two cases by suitable differences of size, brightness or time of exposure; but even under these conditions the sense data would not be the same in direct and indirect vision.

The experiments described in this report do not show that the central factors involved in peripheral form perception are radically different from those operating in direct vision. All that the experiments suggest is that, owing to the blurred nature of peripheral vision produced by retinal and physical factors, already discussed, central processes are more likely to introduce mistakes and illusions into peripheral perception by direct vision.

The concluding sentence in the pamphlet, "on the whole, the experiments do not suggest that there are many radical differences between the central processes influencing peripheral perception and those influencing direct perception," is most significant. The reviewer feels that the entire pamphlet can be read with profit by both neurologists and psychologists, as well as by ophthalmologists.

The other reports were as follows:

No. 104. Illumination and Visual Capacities. By R. J. Lythgoe. Price, 2 shillings, 6 pence. 1926.

No. 127. Dark Adaptation (A Review of the Literature). By Dorothy Adams. Price, 5 shillings. 1929.

No. 130. Two Studies in the Psychology of Reading. By M. D. Vernon and R. W. Pickford. Price, 2 shillings. 1929.

No. 133. Experiments on Binocular Vision. By N. M. S. Langlands. Price, 2 shillings, 6 pence. 1929.

No. 134. The Adaptation of the Eye: Its Relation to the Critical Frequency of Flicker. By R. J. Lythgoe and K. Tansley. Price, 2 shillings, 6 pence. 1929.

No. 136. Some Experiments on Peripheral Vision. By Myer Salaman. Price, 2 shillings, 6 pence. 1929.

No. 139. A Re-Determination of the Trichromatic Mixture Data. By W. D. Wright. Price, 1 shilling, 3 pence. 1929.

No. 148. The Movements of the Eyes in Reading. By M. D. Vernon. Price, 9 pence. 1930.

These reports are obtainable from the British Library of Information, 5 East Forty-Fifth Street, New York.

Die Denkmethoden und ihre Gefahren. By Dr. Vera Strasser. Price, 20 marks. Pp. 526. Leipzig: Georg Thieme, 1931.

Vera Strasser intends to clean up all the artificial mental creations, such as the unconscious with its repressions and displacements, complexes, transferences, demoniac factors and archaisms, and to transvaluate the psychic phenomena which in science and in every-day life have been loaded with false material (feeling, affect, affectivity, instincts, will, thought in terms of causalities and finalities, etc.). Will she "debunk" psychology and psychopathology? She attacks a gigantic task.

She deplores that words and concepts, with much false content however, unfortunately not only act as signs but become symbols for content which ramify from man to man, from generation to generation in science and in ordinary life. She wants to expose the dangerous tendencies by giving an account of the origin and development of the manifold reaching out and mechanisms of thought processes and thought elements, confusions by products which run counter to the somatic-psychic construction, confusion concerning disease entities, concepts of normality and disease and consequently confusion in therapy, and confusion in the conceptions of the world, the sense of life, the sense of death, the impatience of the individual and the many that finally succumb to disease and to suicide. She wants to expose the prevailing relativism in science and average life and to show that there is a unitary measure for the normal and abnormal course of the life processes, and that there are in this sense absolute laws. She thus comes to offer a guide for war on the one-sided orientations and absolutisms which disfigure individual and group life.

The thirty chapter headings are indeed both comprehensive and provocative—one might say a survey of nature and logic. Dr. Strasser takes up the following topics: matter and function; the essence of nature; life and death as mirrored in the thought methods; the psychic capacities and their applications; properties and qualities; the thought methods; causal thinking; finalistic thinking; comparison; organization; the idea; thoughts as points of view; thoughts tending to absolutes; analytic and synthetic thinking in psychology; political and scientific thinking; faith; suggestion; error; leveling; formation of types; the effect of thought methods on the child's mind; their effects on adolescence; woman and her thought methods; the thought methods of the medical psychologists and psychoanalysts, the clinical psychiatrists; the nervous and psychotic *Beziehungskranken* (specifically dementia praecox); problems of crime and instability; temperament; freedom; the absolute as a product of the free utilization of the capacities. A full

index of 18 pages of authors and topics allows one to get a sense of proportion of the mass of material touched on in the 508 solid pages.

The central characteristic of the presentation lies in the emphasis on the *Fähigkeiten*, or a new edition of a faculty concept as capacities and their orchestration. At any rate, one deals with something which indeed lends itself to what others emphasize under the second important positive issue as ideologies, the emphasis on *Denkmethoden*. On the negative side there is a strong aversion to the creations of psychoanalysis, the unconscious, etc., and the psychiatries related to it, as, for instance, that of Bleuler. A similar condemnation hits relativism.

The book is written in an aggressive, critical vein. It covers an unbelievably wide range of material.

The deduction of the positive substitutes for the condemned concepts and formulations is not altogether easy, owing to the breadth and discursiveness of the presentation and the relative dearth of readily controllable observational material. A book by the author dealing specifically with dementia praecox will no doubt meet this demand for concreteness, and may bring an illustration of how the strong tendency to the condemned relativism can be replaced by the author's absolutism.

The Mind: A Key to the Interpretation of Psychical Phenomena. By George E. Rehberger, Phoenix, Md. Pp. 214. Baltimore: Lord Baltimore Press, 1931.

An ambitious attempt to explain all mental phenomena is embodied in this small book. "Suggestion" is considered by the author to be one of the most important concepts in psychology. The term recurs frequently in the text, and is used to account for most mental reactions, both normal and abnormal. Thus, the author says that "negativism is unrestrained negative suggestibility" (p. 125). What precisely he means by suggestion or "suggestional activities" does not become entirely clear. He seems to regard it as a sort of physiologic process, as when he says that "the progress of suggestion is the progress of an impulse through synapses or nervous tissue" (p. 148).

The author is apparently much influenced by a dream experience which he had in 1930. He dreamed of cavalry men slashing with sharp, cutting sabers. When he awoke, he was conscious of "acutely cold shoulder tips" (p. 20). He seems to regard this connection between the dream content and a physical stimulus (which he terms "suggestion") as a new observation. As a matter of fact, such relationships have been frequently recorded, as, for example, in the famous "guillotine dream" published by Maury in 1878.

Many of the statements in this book are on the borderline between platitudes, half-truths and pure speculation. Where the author makes explicit and clear statements he is frequently wrong, as when he says, "There is no more reason why a praecox patient should not also have manic-depressive psychosis than that he should not contract measles" (p. 189); "Our normal mood is one of slight depression" (p. 193), or "Hallucinosis is always a schizophrenic process" (p. 196).

This book is intended apparently for the general reader, and has no scientific interest. As literary references the author cites the following: "The Textbook of Psychology," by Gates, "Psychology of Insanity," by Bernard Hart, and the Correspondence Course of the United States Army School of Aviation Medicine, Brooks Field, San Antonio, Texas.

Persönlichkeitsentwicklung und Wahnbildung: Eine Untersuchung über den Sinn des Erlebens und die Bedeutung des Verhaltens bei den krankhaften Veränderungen des Ich. By Walter Betzendahl. Price, 16 marks. Pp. 321. Berlin: S. Karger, 1932.

The bulk of this monograph consists of the extremely full and detailed presentation of eight case histories. The patients in question suffered from severe schizophrenic psychoses. In the first two cases, a tendency to regain social relationships was evident. The last two patients were free from delusions and had no actual

conflict with the environment, but could be provoked suddenly to definitely paranoid reactions. The remaining histories are intended to show what the author considers the chief directions of the psychotic process.

The author's comments on these extensive case records are difficult to read and somewhat abstruse. It does not become entirely clear what is the goal of his presentation. He evidently wishes to convey the idea that in themselves the experiences and reactions of these patients are not understandable to normal persons; they have a meaning and this meaning grows out of the premorbid personality of the patient. "When the patient omits systematization, it [systemization] becomes the task of the psychiatrist" (p. 5). Emphatic understanding of endogenic psychoses is impossible, "for in this way the morbid element, which forms the kernel of the whole thing, is left out" (p. 302).

The reviewer confesses that it is difficult for him to estimate the significance of this volume. It impresses him as the raw material—or, at best, the first draft —of a monograph that remains to be written.

Witchcraft, Magic and Alchemy. By Grillot de Givry. Price, $10. Pp. 395, with 10 plates and 366 illustrations. Boston: Houghton Mifflin Company, 1931.

This volume fills a distinct gap in the literature of today. Since it is generally acknowledged that numerous analogies can be drawn between the behavior of neurotic patients and many kinds of superstitions, rituals and magic practices, psychopathologists have become more and more interested in recent years in the behavior of primitive people. Insufficient attention has been given, however, to the primitive practices that are prevalent among civilized people. There is a large, nonscientific literature on this subject, but it is not easily accessible, and reliable books on the subject are scarce.

This book is a scholarly work devoted to what have been called the occult or secret sciences of the past. It confines itself to European tradition. Among the subjects dealt with are the following: diabolic manifestations in the religious life, the witches' Sabbath, the evocation of demons, pacts with demons, possession, necromancy, philters and spells, astrology, chiromancy, cartomancy, alchemy and the (occult) interpretation of dreams.

As an introduction to the original source books on the subject, this book is practically indispensable. It contains many details which are of great interest to the psychiatrist and which cannot be overlooked in the formation and criticism of the theories of mental aberration. The chapters on the mystery of sleep and clairvoyance and "curative virtues of the invisible forces" are of special and direct interest to the psychopathologist. There are many illustrations, reproductions of old paintings and engravings, which in themselves constitute an introduction to the subject.

Fleckfieber und Nervensystem. By Nikolai Hirschberg. Price, 11.60 marks. Pp. 124. Berlin: S. Karger, 1932.

This volume is a comprehensive presentation of the disorders of the central and peripheral nervous system found in spotted fever. The author was the first to describe the psychoses occurring in spotted fever, observations based on the epidemic in Moscow in 1910. In the present volume he surveys the whole field indicated. The subject matter is divided into the following chapters: pathologic anatomy, peripheral nerves, sympathetic nervous system, cerebrospinal fluid and meninges, spinal cord, brain stem, acute ataxia, cerebrum, basal ganglia and mental disorders. The neurologic and psychiatric symptomatology is minutely described. The author believes that the results of histopathologic investigations have alone made it possible to understand the manifestations of this infectious disease, in which symptoms on the part of the nervous system are in the foreground. He is perhaps inclined to overrate the significance of the small glial foci for correlation with clinical symptoms. Thus, he seems to agree with Förster's correla-

tion of chorea in spotted fever with the occurrence of such glial foci in the diencephalon, the brachia conjunctiva and the lenticular nucleus. But this sort of glial lesion may occur anywhere in the central nervous system, and, moreover, it is found in conditions in which clinical symptoms referable to the central nervous system are absent.

The book is clearly written and has a good bibliography. It is a credit to Russian neuropsychiatry and deserves the best recommendation.

Psychologie und aertszliche Praxis. By Herman F. Hoffmann. Price, 2.80 marks. Pp. 67. Berlin: Julius Springer, 1932.

This small book is addressed to the general practitioner. The author reviews briefly the chief types of neurotic disorders. He discusses some of the outstanding conflicts that may occur during the life of an individual man and adds a discussion of some of the main psychologic facts that are to be found in the structure of the common types of nervous disorders. There is also a short statement concerning the so-called compensation neuroses. The conclusion is taken up by a brief reference to therapy.

The book makes no new contribution and remains, on the whole, rather on the surface of the subjects discussed. Although psychoanalytic trains of thought are frequently alluded to, psychoanalytic terms are carefully avoided. The psychosexual life is treated too inadequately, even for such a small book. Since there are no references to the literature, the general practitioner who wishes to gain further information about the subjects indicated in this brief survey is apt to find himself somewhat at a loss.

The Wisdom of the Body. By Walter B. Cannon, M.D. Price, $3.50. Pp. 312. New York: W. W. Norton & Company, Inc., 1932.

Under the ambiguous title of "The Wisdom of the Body," the author writes of the relation of the autonomic system to the self-regulation of physiologic processes. The main features were first presented in a technical article in *Physiological Reviews* in 1929, under the title, "Organization for Physiological Homeostasis," in the Linacre Lecture for 1930, and in a series of lectures in the winter of 1930 before the Sorbonne. This work is supplementary to two previous books by the same author, "Bodily Changes in Pain, Hunger, Fear and Rage" and "Traumatic Shock." The book is written for the general reader, but while there is no question that parts of it would be of interest, it is questionable whether the general reader has sufficient information to be able to understand its contents. To the reviewer the presentation was fascinating and was read as easily as a novel, for the facts are excellently put forth and so arranged that one cannot help obtain a great deal of information.

Neurology. Edited by Peter Bassoe, M.D. **Psychiatry.** Edited by Franklin G. Ebaugh, M.D. The Practical Medicine Series, 1931. Price, $2.25. Pp. 450. Chicago: Year Book Publishers, Inc., 1932.

"The Practical Medicine Series" on neurology and psychiatry for 1931 is up to the previous high standards maintained by this publication. It was originally edited by Patrick of Chicago, but it has been equally well done by Peter Bassoe. This year the editorship has been divided, in that Franklin G. Ebaugh reviewed the psychiatric material.